MEDICAL REVIEW

NDA No.: 20-386/SE1-028
DRUG NAME: COZAAR™ Tablets (Losartan Potassium)
SPONSOR: Merck & Co., Inc.
West Point, Pennsylvania 19486
TYPE OF DOCUMENT: New Drug Application-Efficacy Supplement
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MEDICAL REVIEWER: Juan Carlos Pelayo, M.D.

INTRODUCTION AND BACKGROUND

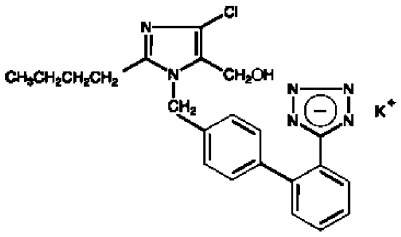
The prevalence of end-stage renal disease continues to increase in the United States; currently it is approximately twice what it was a decade ago. [1] This increase spans all racial and ethnic groups, however Hispanics, Native Americans, and Blacks carry a risk that range from two to more than four times those of whites. Diabetic nephropathy is the leading cause of end-stage renal disease in the United States and is a significant health problem because of the resultant morbidity and mortality. Of note, renal disease due to type 2 diabetes appears to account for almost all of the increasing number of patients with kidney failure. In only 10% to 15% of patients with type 2 diabetes mellitus does end-stage renal disease develop, however type 2 diabetes accounts for approximately 50% of end-stage renal disease cases with diabetic nephropathy since 85% of all patients with diabetes have type 2. Hence, the discovery of therapeutic interventions aim to prevent/attenuate the progression of diabetic nephropathy due to type 2 diabetes to end-stage renal disease is a public health priority. Patients with type 2 diabetes mellitus have a high prevalence of hypertension. In this regard, epidemiological data and results from clinical trials suggest that strict glycemic and blood pressure control blunt its renal complications.

Hitherto, there is not a drug approved by the FDA for the treatment of renal disease due to type 2 diabetes mellitus. Captopril, an angiotensin converting enzyme inhibitor, is the only drug to gain FDA's approval for the treatment of diabetic nephropathy but only for those patients with renal disease due to type 1 diabetes mellitus.

Based on the results from pre-clinical as well as clinical studies the sponsor reasoned that losartan, via hemodynamic and non-hemodynamic mechanisms through blockade of the renin-angiotensin system in addition to the antihypertensive action, could effect a treatment benefit to normotensive or hypertensive patients with type 2 diabetes and nephropathy like that observed with captopril in patients with renal disease due to type 1 diabetes mellitus.[2] To test the hypothesis Merck & Co. Inc. sponsored the clinical development of COZAAR™ (Losartan Potassium) in normotensive as well as hypertensive patients with diabetic renal disease due to type 2 diabetes mellitus. In essence, the clinical development program of losartan consists of one pivotal clinical trial.[3] The results from this investigation were published in the *New England Journal of Medicine*[4] and submitted to the FDA by the sponsor as an efficacy supplement (SE1-028) to NDA 20-386.

GENERAL INFORMATION

Drug name: COZAAR™ (Losartan Potassium). Losartan is a non-peptide molecule, chemically described as 2-butyl-4-chloro-1-[*p*-(*o* -1*H*-tetrazol-5-ylphenyl) benzyl]imidazole-5-methanol monopotassium salt. Its empirical formula is C_{22} H_{22} $ClKN_6$ O, and its structural formula is:



[1] U.S. Renal Data System. USRDS 2001 Annual Data Report: atlas of end-stage renal disease in the United States. Bethesda, Md.: National Institute of Diabetes and Digestive and Kidney Diseases, 2001. Hostetter TH. Prevention of end-stage renal disease due to type 2 diabetes. N Engl J Med 2001;345:910-912. Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. N Engl J Med 1999;341:1127-33.
[2] Lewis EJ, *et al*. The Effect of Angiotensin-Converting-Enzyme Inhibition on Diabetic Nephropathy. N Engl J Med 1993;329:1456-62.
[3] A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Renal Protective Effects of Losartan in Patients with Non-Insulin Dependent Diabetes Mellitus and Nephropathy (RENAAL).
[4] Brenner, BM, *et al*. Effects Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy. N Engl J Med 2001;345:861-9.

Drug Class: COZAAR™ is an angiotensin II receptor antagonist with a much greater affinity (more than 1000-fold) for the AT_1 receptor than for the AT_2 receptor and no agonist activity. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor and its active carboxylic metabolite (E-3174) is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT_1 receptor.

Sponsor's Proposed Indication(s): COZAAR™ is approved "for the treatment of hypertension" regardless etiology. "It may be used alone or in combination with other antihypertensive agents."[5]

The sponsor is now seeking a new indication: *Renal Protection in Type 2 Diabetic Patients with proteinuria* "COZAAR™ is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, and end-stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria."

Dose and Regimens: COZAAR™ is available for oral administration in tablets containing 25 mg, 50 mg or 100 mg of losartan. The current recommended initial dose of COZAAR™ in hypertensive patients is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume and patients with a history of hepatic impairment. COZAAR™ can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

The sponsor recommends in patients with type 2 diabetic renal disease 50 mg once daily as the starting dose, and this dose may be increased to 100 mg once daily based on blood pressure response.

COZAAR™ in Pediatric Population: The study submitted in support of this supplemental NDA did not evaluate patients within the pediatric age groups. Pursuant to 21 CFR 314.55 (c), Merck & Co., Inc requested a full waiver to the pediatric data requirement for the treatment of pediatric patients with type 2 diabetes and nephropathy. "The rationale for this full waiver request is that the proposed indication does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients. Although type 2 diabetes may develop in adolescents, the complication of diabetic nephropathy develops 5-10 years after the onset of disease. Thus, such patients generally would be young adults by the time nephropathy occurred and treatment with losartan could be started to delay progression of their underlying disease (per the proposed indication)."

Post-Marketing Experience: COZAAR™ was approved in United States of America on April 14, 1995, since then several countries worldwide have approved it for the treatment of hypertension.

CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS AND/OR OTHER CONSULTANT REVIEWS

The medical reviewer relied on the results of the statistical analyses by Dr. Hsien Ming J Hung (FDA, HFD-710) for the evaluation of the clinical data.

HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

Not applicable.

[5] As per the current label for COZAAR™ Tablets (Losartan Potassium).

DESCRIPTION OF CLINICAL DATA AND SOURCES

The clinical development program of losartan consists of one international, multicenter, randomized, double-blind, placebo-controlled safety and efficacy study in normotensive/hypertensive patients with diabetic renal disease due to type 2 diabetes (Protocol No. 147. A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Renal Protective Effects of Losartan in Patients with Noninsulin Dependent Diabetes Mellitus and Nephropathy, RENAAL study). Hence, any regulatory action on COZAAR™ (Losartan Potassium) for the new sought indication "*Renal Protection in Type 2 Diabetic Patients with proteinuria"* depends on the interpretation of the results from this study.

The RENAAL study evaluated 1513 normotensive/hypertensive patients with type 2 diabetes and nephropathy, who were randomized from 250 investigative centers in 29 countries from Europe, Asia, Latin and North America. The study investigated whether losartan, either alone or in combination with conventional antihypertensive therapy (diuretics, calcium channel blockers, beta blockers, alpha blockers, and centrally acting agents), reduced the number of patients with type 2 diabetes experiencing a doubling of serum creatinine, ESRD, or death compared to placebo-treated patients (with or without conventional antihypertensive therapy). In addition, the study assessed the effects of losartan (versus placebo) on cardiovascular morbidity and mortality, progression of renal disease measured as the slope of the reciprocal of serum creatinine, and changes in proteinuria. Other parameters measured included quality of life (U.S. patients only) and healthcare resource utilization (U.S. and European patients only). The trial was conducted in accordance with accepted Ethical Standards.

The following materials were used in the medical review: hard desk copies, electronically submitted materials (electronic archive including SAS data files), and sponsor's responses to specific FDA's requests for further information and/or clarification of data.

DOSING, REGIMEN, AND ADMINISTRATION ISSUES

RENAAL is the only trial submitted by the sponsor where the effect of COZAAR™ (Losartan Potassium), up to 100 mg, on renal and cardiovascular morbidity and all-cause mortality was evaluated in patients with renal disease due to type 2 diabetes mellitus. The percentage of patients who took the designated daily dose of losartan more than 50% of the time is as follows: 1.6% took 25 mg, 26.6% took 50 mg and 71.8% took 100 mg. The results from the RENAAL study indicate that losartan given daily significantly increased the time to doubling of serum creatinine, as compared with placebo. Based on the above results, if COZAAR™ (Losartan Potassium) is approved for the treatment of subjects with diabetic nephropathy due to type 2 diabetes, 100 mg daily should be the recommended dosage regimen. There are no new issues arising from the RENAAL study with regard to the administration of losartan.

USE IN SPECIAL POPULATIONS

The population in the RENAAL study predominantly consisted of white (48.6%) males (63.2%) under the age of 65 years (66.4%). Females, subjects >65 years of age, as well as Hispanics, Native Americans, Blacks, Asians and other races were significantly underrepresented in the clinical trial, and subjects within pediatric age groups were not randomized into the study. Hence, the retrospective nature of the subgroup analysis together with the lack of statistical power for such analysis precludes any valid conclusion on the use of losartan in special populations.

SUMMARY/CONCLUSIONS

The clinical development program of losartan consists of a single pivotal clinical trial, the RENAAL study. Hence, any regulatory action on COZAAR™ (Losartan Potassium) for the new sought indication "*Renal Protection in Type 2 Diabetic Patients with proteinuria"* hinges primarily on the interpretation of the results from that study.

It seems that the regulatory obstacle to overcome before a decision is made is whether and why the RENAAL study, a single clinical trial showing a modest treatment benefit primarily through a surrogate endpoint with a marginal p-value[6] and without confirmatory evidence, is insufficient for approval. What follows is a summary of efficacy highlighting the consistency of the results and design features of the study critical to their interpretation, and ancillary as well as complementary information that together dispel the notion that the results of the RENAAL study are insufficient to warrant approval.

Efficacy: A total of 1513 subjects (losartan n=751 and placebo n=762), with overt nephropathy due to type 2 diabetes mellitus, were randomized into the clinical trial. The population was predominantly white (48.6%), males (63.2%), under the age of 65 years (66.4%) with a mean BMI of 29.7%. 96.6% of the subjects were hypertensive at study entry. The mean baseline seated systolic and diastolic blood pressures were 152.5 mmHg and 82.4 mmHg, respectively. Mean serum creatinine was 1.9 mg/dl and mean proteinuria (UA/Cr) was 1808 mg/gCr. Ninety percent of the patients had diabetes for ≥5 years, and 60.1% and 49.0% had used insulin and oral anti-diabetics prior to study entry, respectively. Mean $HbA1_c$ was 8.5%.

Based on comparison of the means, there were no significant differences/imbalances between the treatment groups in baseline demographic characteristics, blood pressure, prior therapies, and laboratory measures that could potentially obscure the interpretation of the study's results.

The RENAAL study demonstrated a modest treatment benefit for losartan in hypertensive patients[7] with advanced diabetic nephropathy due to type 2 diabetes mellitus. The risk of the primary endpoint, a composite outcome variable of time to first event of doubling serum creatinine, ESRD or death[8], was significantly reduced by losartan treatment, the relative risk reduction was 16.1% with a marginal p-value equal to 0.022. An analysis of the primary endpoint by country indicates that there was not significant regional heterogeneity.

Albeit the study was not powered to detect differences between treatments for the components of the primary endpoint, the treatment benefit is explained entirely by a delay in the time to doubling of serum creatinine. The risk of the component of doubling of serum creatinine was reduced by 25.3% (95.2% CI 0.61, 0.92; p=0.006) in losartan-treated subjects. Losartan treatment had no effect on time to ESRD (p=0.66) or death (p=0.91). This outcome is not unexpected because in the study's inclusion criteria a serum creatinine ≤3.0 mg/dl corresponded to the maximum value for study entry, for both males and females subjects, so a value equal to 6.0 mg/dl albeit means a doubling as a rule does not establish ESRD prompting dialysis or renal transplantation. Therefore, one could have predicted that the treatment effect would be primarily an effect on doubling of serum creatinine. Also the study was not powered to separately assess an effect on mortality. Nevertheless, the risk of the composite endpoint of ESRD or death was reduced by 19.9% in patients receiving losartan (p=0.009, 255 (34.0%) events for losartan and 300 (39.4%) for placebo, hazard ratio 0.8 and CI 0.68, 0.95).[9]

It should be noticed that even though doubling of serum creatinine is a surrogate of clinical benefit, the FDA's perspective on the subject is that of a validated surrogate endpoint. In view of that, the observed differences in

[6] Currently, the Division of Cardio-Renal Drug Products advises sponsors that approval of a drug, requires two trials with the primary endpoint tested at a p-value = 0.05 or one trial with a p-value = 0.00125. However, at the End-of-Phase II Meeting, dated March 8, 1996, the FDA did not address this subject with the sponsor.
[7] In reality, this clinical investigation evaluated the renal protective effect of losartan almost uniquely in hypertensive patients because >95% of the randomized subjects had hypertension at study entry.
[8] The definition of the primary endpoint had the concordance of the FDA from the inception of the study (End-of-Phase II Meeting, dated March 8, 1996).
[9] This was a pre-specified analysis of the primary endpoint. The results were verified by Dr. Hung (FDA, HFD-710.)

doubling of serum creatinine should weigh in the regulatory decision the same as differences in ESRD events. A retrospective analysis of the total incidence for the morbid and mortal components of the primary composite endpoint lends support to the aforementioned notion. Albeit losartan treatment did not affect mortality (158 *vs.* 155 deaths, p=0.884, 95.2% confidence interval 0.81, 1.27), losartan-treated patients had significantly fewer ESRD events throughout the trial as compared with those subjects in the placebo group, 147 *vs.* 194, respectively (p=0.002, risk reduction of 28.6%, 95.2% confidence interval 0.57, 0.89). The difference in the number of ESRD events between the groups is forty-seven. According to the sponsor, of the subjects who had a doubling of baseline serum creatinine, 51% *vs.* 65% developed ESRD in the losartan and placebo groups, respectively. These analyses significantly strengthen the evidence in support of a renal protective effect of losartan in subjects with type 2 diabetes mellitus and overt nephropathy.

Subgroup analysis of the primary endpoint by demographic variables or baseline factors is of interest, but its retrospective nature together with the lack of statistical power preclude any valid conclusion on the use of losartan in special populations.

In keeping with the results on doubling of serum creatinine and ESRD, losartan-treated patients lost renal function at a rate[10] significantly lower than patients receiving placebo did (estimated reduction in the rate of decline in renal function 12.7%, p=0.0091). Also, losartan treatment reduced proteinuria to a greater extent than placebo, on average 33%, and this effect was statistically significant at month 3 through month 39 ($p<0.001$) and at month 42 ($p<0.01$). Of interest, the sponsor conducted a retrospective analysis to ascertain the effect of baseline proteinuria on the progression of renal disease, in comparison to placebo, losartan had a significant beneficial effect only in patients who had proteinuria ≥2000 mg/gCr (p=0.042 for patients with proteinuria between 2000 and 3000 mg/gCr, and p=0.019 for patients with proteinuria ≥3000 mg/gCr).

The results of the intent-to-treat analysis of the secondary composite endpoint of cardiovascular morbidity/mortality, pre-specified as the time to first event of myocardial infarction, stroke, hospitalization for heart failure or unstable angina, coronary or peripheral revascularization, or cardiovascular deaths, indicate that losartan administration failed to effect a treatment benefit. The estimated risk reduction (losartan *vs.* placebo) was 9.6% (95% confidence interval -7.5%, 24.0%, p=0.253). Losartan only reduced the risk for hospitalization for heart failure (total incidence) by 31.6% (89 patients with losartan *vs.* 126 with placebo; hazard ratio 0.68, p=0.006). Again it is worth mentioning that the study was not powered to evaluate the effect of losartan on cardiovascular morbidity/mortality.

Treatment with losartan as compared with placebo did not significantly affect the rate of amputation and failed to improve quality of life.

The study was not well controlled in that the groups had statistically significant dissimilar blood pressure levels almost throughout the duration of the trial. Noteworthy, the losartan group had significantly lower mean blood pressure levels than the placebo group did [range -0.89 to -3.55 mmHg, mean (±SD) -2.29 (±0.74) mmHg]. Contrary to the current belief, statistical adjustment(s) for differences in blood pressure control is not plausible because at present a quantitative description of the relationship between blood pressure and progression of renal disease due to diabetes mellitus remains intangible. Thus, the contribution of a greater blood pressure control to the overall renal protective effect of losartan can not be determined.[11]

Glycemic control based on $HbA1_c$ levels was comparable between the groups.

At this point, commentary on ancillary as well as complementary information to the RENAAL study is in order. To reiterate, hitherto, there is not a drug approved by the FDA for the treatment of the nephropathy associated with type 2 diabetes mellitus. Captopril, an angiotensin converting enzyme inhibitor, is the only drug to gain FDA's approval for the treatment of diabetic nephropathy but only for those patients with overt nephropathy due to type 1 diabetes mellitus. The captopril study, performed over a decade ago, is heralded as the "gold

[10] Determined by the slope of the reciprocal of serum creatinine (1/sCr) across time (year) during the trial.
[11] Of note, the captopril study and the study with another angiotensin II receptor antagonist in patients with nephropathy due to type 2 diabetes had comparable discrepancy in blood pressure control, that is the subjects receiving the test drugs had significantly lower blood pressures than those placebo-treated subjects.

standard" of clinical trials for diabetic nephropathy. And the prevailing view is that new clinical trials investigating treatments for diabetic nephropathy have to measure up to its results. The study had three primary endpoints a) total incidence of doubling of serum creatinine, b) the rate of urine protein excretion and c) total incidence of ESRD or death. The results are as follows: doubling of serum creatinine was reached by 43 of 202 placebo and 25 of 207 captopril subjects (RR=51.1%, p=0.004); ESRD was reached by 31 placebo and 20 captopril subjects (RR=41.9%, p=0.055); deaths occurred to 14 of 202 placebo and 8 of 207 captopril subjects (RR=46.6%, p=0.150); ESRD or death was reached by 42 of 202 placebo subjects and by 23 of 207 captopril subjects (RR=50.5%, p=0.006).[12] Noteworthy, there was a significant imbalance in the rate of urinary protein excretion at baseline, proteinuria was significantly lower in the captopril group than in the placebo group ($p<0.02$). How this major baseline difference may have affected the study's outcome is uncertain. Perusal of the above results indicates that they are qualitatively similar but quantitatively, i.e., the magnitude of the effect, larger as compared to the RENAAL study. However, to draw conclusions from that comparison lacks scientific rigor because among others the captopril study was carried out over a decade ago. Since then the treatment of patients with diabetes mellitus have significantly evolved, namely more strict glycemic and blood pressure control, use of different antihypertensives combination, use of lipid lowering agents, etc., which in and of itself could have alter the responsiveness of the disease to therapeutic interventions. Thus whether one could replicate today the results of the captopril study, in particular as it relates to the magnitude of the effect, in patients with nephropathy due to type 2 diabetes is uncertain at best.

Finally, it is important to mention that the RENAAL study is not the only clinical investigation that had evaluated the effect(s) of an angiotensin II antagonist on the progressive nature of the nephropathy associated with type 2 diabetes mellitus. The IDNT study[13], which its results were published at the same time as the RENAAL study, demonstrated a treatment benefit for another AII antagonist in hypertensive patients with advanced diabetic nephropathy due to type 2 diabetes. The primary composite endpoint was time to first event of doubling of serum creatinine, ESRD, or death, the AII antagonist significantly reduced the risk of the primary composite endpoint (relative risk reduction of 20%, p=0.0234 *vs.* placebo and relative risk reduction of 23%, p=0.0064 *vs.* Amlodipine). Thus the results from the IDNT and RENAAL studies complement each other, lending support to the developing notion of a drug class effect.

Safety: The safety profile of losartan that emerged from the evaluation of the RENAAL study primarily in hypertensive subjects with advanced nephropathy due to type 2 diabetes mellitus is comparable to the safety profile delineated already in patients with hypertension regardless causality. Overall losartan was well tolerated and safe; there are no new safety concerns regarding the use of losartan in this diabetic population.

A risk-benefit analysis based on the available empirical data supports the notion that losartan administration is associated with a treatment benefit, delays the progression of diabetic nephropathy, without significant safety risks.

RECOMMENDATIONS

The recommendation is that COZAAR™ (Losartan Potassium) be approved for the treatment of hypertensive patients with overt nephropathy due to type 2 diabetes mellitus.[14]

[12] The information was obtained from the FDA's primary medical review of the captopril study, dated October 14, 1993.
[13] Lewis, EJ, *et al*. Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes. N Engl J Med 2001;345:851-60. The results of the IDNT study were discussed at the Cardio-Renal Advisory Committee Meeting on January 17, 2002.
[14] The labeling for losartan should be modified to reflect the results of the RENAAL study.

STUDY REVIEW

Protocol No. 147. A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Renal Protective Effects of Losartan in Patients with Noninsulin Dependent Diabetes Mellitus and Nephropathy (RENAAL)

INVESTIGATIONAL PLAN

Study Design: This was a double-blind, randomized, placebo (±conventional non-ACE inhibitor, non-AIIA antihypertensive therapy) controlled, multinational, multicenter long-term study to determine the effect of losartan (±conventional non-ACE inhibitor, non-AIIA antihypertensive therapy) on renal and cardiovascular endpoints in normotensive and hypertensive patients with type 2 diabetes and nephropathy. Following a 6-week screening period, eligible patients were stratified by baseline level of proteinuria, i.e., urine albumin to urine creatinine ratio (UA/Cr) from a first morning void above or below 2000 mg/g Cr, and randomized 1:1 to either losartan 50 mg or placebo on a background of conventional antihypertensive therapy (ACE inhibitor or AIIA therapy excluded). After the first month of double-blind therapy if trough blood pressure did not reach the goal of <140/90 mmHg losartan was to be increased to 100 mg daily (2 tablets of study drug).[15] Patients were to receive double-blind therapy for approximately 4.5 years.

As recommended by the American Diabetes Association patients were encouraged to follow a 0.8 mg/kg/day protein and 2,000 mg/day or less sodium diet.

With the exception of ACE inhibitors and angiotensin II antagonists, prior and concomitant use of conventional antihypertensives was permitted. Short-term use of NSAIDs, steroids or immunosuppressives was allowed on a case-by-case basis if medically warranted.

Study Population: Male and female patients between 31 and 70 years of age, with type 2 diabetes and proteinuria (an albumin to creatinine ratio of ≥300 mg/g), with serum creatinine levels between 1.5 to 3.0 mg/dl for males and 1.3 to 3.0 mg/dl for all females and males <60 kg, with or without hypertension (Sitting BP ≤200/110 mmHg) were enrolled in the study.[16]

Efficacy Variables: The primary composite endpoint is time to the first event of doubling of serum creatinine, ESRD, or death due to any cause. Doubling of serum creatinine is defined as a twofold increase from baseline (average of the last two prerandomization values); the first value which defines this doubling must be confirmed (i.e., remain doubled) by a repeat measurement taken approximately 4 weeks after the first doubling has been observed. ESRD is defined as the need for chronic dialysis or renal transplantation.

The time to first event of the composite endpoint of cardiovascular morbidity/mortality is the secondary endpoint. Cardiovascular morbidity/ mortality is defined as: death due to cardiovascular disease, nonfatal MI, nonfatal stroke, unstable angina requiring hospitalization, heart failure requiring hospitalization, and need for coronary or peripheral revascularization. Changes from baseline (average of last two prerandomization values) in the ratio of urine albumin to urine creatinine is the other secondary endpoint. Progression of renal disease as measured by the reciprocal of serum creatinine is also a secondary endpoint.

Tertiary endpoints are quality of life (U.S. only), healthcare resource utilization (U.S. and Europe), and incidence of amputations.

A pre-specified interim analysis of the primary composite endpoint was performed for review by the DSMB

[15] If necessary, the patient's usual antihypertensive drug therapy should be increased, or, any of the following open-label antihypertensive agents added at the discretion of the investigator to obtain the target blood pressure: a diuretic, a beta-blocker, a calcium channel blocker, an alpha-blocker or a centrally acting agent. Of note, angiotensin converting enzyme inhibitors and other angiotensin II antagonists were excluded from the trial.

[16] For a complete description of this study's protocol the reader is referred to NDA20-386/SE1-028, Protocol No. 147.

only when one-half of the expected number of endpoints was reached.

Safety: Clinical and laboratory data were collected every 3 months.[17] Patients who discontinued early from study therapy continued to be followed in the clinic every 3 months, or by telephone contact if they could not visit the clinic, until the end of the study.

Treatment Compliance: Drug dispensing information was recorded on a drug accountability worksheet at each visit. A tablet count was also performed when study drug was returned at each visit and recorded on the drug accountability worksheet. The patient was questioned about compliance if the tablet count was not consistent with the number of days between visits. The sponsor defined compliance "as taking study drug >80% of the time during the double-blind treatment."

Statistical Methods: The sample size calculation for this trial is based upon the assumption that the 5-year doubling of serum creatinine/ESRD/death rate in the placebo group will be 58% and that this rate will be reduced by 20% (absolute proportion of 46.4%) in the losartan group. The predicted doubling of serum creatinine, ESRD and death event rates in the placebo group are based upon unpublished data from two NIDDM cohorts. Ninety-five percent (95%) lower confidence bounds of the first-event rates were used for sample size estimation to account for variability of the estimates and improvement in disease management (e.g., better glucose control, higher use of lipid-lowering agents). An additional adjustment (increase) was made to the doubling and ESRD event rates to account for the inclusion of higher risk patients that were not represented in the cohorts. Based upon the assumed event rate and treatment effect, in order to have at least 95% power at the 4.9% significance level (two-sided, adjusted for interim analysis), the trial should enroll at least 1520 patients and continue until the last enrolled patient has been followed for 4 years. The sample size estimate has also assumed the following: patients will be entered at a uniform rate during a 1-year enrollment period, the treatments will have proportional hazards, and that 50% of the patients will discontinue double-blind study therapy during the course of the trial (13% per year) for reasons other than the primary endpoints.

The primary approach that will be used for all efficacy and safety analyses is the "intent-to-treat" approach.

Study Administrative Structure: The study was overseen by an independent Steering Committee, who were blinded to the data throughout the duration of the study. An independent, blinded Endpoint Committee adjudicated all endpoints and an independent Data Safety Monitoring Board (DSMB), who were unblinded, monitored the safety of the study on a regular basis. The DSMB was responsible for identifying safety issues and interpreting emerging study data at the interim analyses.

RESULTS

Interim monitoring and Analysis: "The study was planned to be completed in Mar-2002, 4.5 years from last patient in. However, the Steering Committee, whose obligation was to stay abreast of current research in the field and continually re-evaluate the ethical context of the trial, voted unanimously to end the study early, for reasons unrelated to the study data. The reason for this decision was documented in the minutes of the Steering Committee meeting on 10-Feb-2001 and is described in the following paragraph taken from a letter that was sent to all investigators: "At its meeting on 10-Feb-2001, the RENAAL Steering Committee took this action due to increasing evidence that ACE inhibitors are effective in reducing cardiovascular events in patients with characteristics similar to RENAAL patients. This decision to discontinue was in part due to soon-to-be published information showing that cardiovascular events are reduced by ACE inhibitors in diabetic patients with renal impairment. The action of the Steering Committee was taken on the basis of external evidence only and was therefore independent of any knowledge of the results of the trial. The Steering Committee has been and will remain blinded until the results of the trial are analyzed and presented. The Committee further recommended that physicians caring for patients in the RENAAL trial make this information available to their patients and strongly consider addition of therapy aimed at blockade of the renin-angiotensin-aldosterone system (RAAS). In the usual care arm of the RENAAL Study, patients were receiving antihypertensive therapy,

[17] See attached tables (Appendix, pages 32 and 33): Schedule of Clinical Observations and Laboratory Measurements.

excluding agents that block the RAAS. The "soon-to-be published information" referred to the renal insufficiency sup-population of the Heart Outcomes Prevention Evaluation (HOPE) study (with or without diabetes) which demonstrated that use of an ACE inhibitor reduced cardiovascular events."

The endpoint cutoff date for this study was 10-Feb-2001, i.e., any endpoint occurring on or before 10-Feb-2001 was adjudicated.

Amendments: The original protocol was amended 6 times.[18] Significant amendments to the design of the study included:

Amendment No.: 03

1. A new secondary hypothesis and objective is added to assess the effect of losartan on progression of renal disease as measured by the reciprocal of serum creatinine.
2. Data Analysis

a. Sample size: The originally approved protocol was designed to enroll 1520 patients giving at least 95% power (actual power is 97%) for the primary endpoint. Since patient enrollment has been slower than anticipated in the protocol, recruitment of 1520 patients will not be achieved in the projected timeframe. An enrollment period of approximately 2 years is estimated to allow recruitment of at least 1320 patients, the sample size required to achieve 95% power. Therefore, using a 2-year enrollment cutoff, 1320 to 1400 patients will be enrolled which will provide at least 95% power.

b. Duration of follow-up: The original study was planned to have a 1-year enrollment period, with a follow-up period of 4 years from the time the last patient is randomized (an average follow-up of 4.5 years assuming a uniform enrollment pattern). Since the actual enrollment period has been extended to 2 years, the duration of follow-up is reduced to 3.5 years in order to maintain the average follow-tip of 4.5 years, while the study's power is preserved at 95%.

c. The interim analysis stopping rules are updated.

Amendment No.: 04

1. Clarification of the definition of doubling of serum creatinine and time frame for confirmatory value.

a. The initial doubling of serum creatinine measurement may be obtained from the local laboratory or the central laboratory. However, the confirmatory value must be obtained from the central laboratory (Smith Kline Beecham Laboratories).

b. The time period for the confirmatory value should be no earlier than 4 weeks after the initial doubling value was obtained.

2. Definition of ESRD

a. To include patients requiring chronic dialysis but refusing initiation of dialysis and or dialysis is not readily available.

b. The need for dialysis refers to patients with a need for chronic dialysis.

3. Definition of patient follow-up:

Because this is a long-term study, some patients will inevitably discontinue study therapy or become lost to follow-up for various reasons. Because the protocol utilizes the intent-to-treat analysis, endpoint information for patients who have discontinued is imperative. Therefore, telephone follow-up, whenever possible, will be used for patients who discontinued from study drug and are unable/refuse to come to the clinic for protocol scheduled visits. For those patients who refuse telephone follow-up or appear lost to follow-up, public records may be used to obtain primary endpoint information (i.e., ESRD or death).

Telephone Follow-Up: Patients who have discontinued study drug and will not be followed at regular clinic visits will he asked if they agree to phone contact every 3 months. Calls will be based from the date of randomization in an attempt to maintain the patient's visit schedule per protocol. Abbreviated information on the primary endpoints and date of dialysis, transplantation, or death will be obtained.

Lost to Follow-Up: For patients who refuse phone contact or are lost to follow-up, public database searches, i.e., governmental databases such as Healthcare Financing Administration (HCFA) and the National Death Index (NDI) in the United States, will be necessary to determine the status of patients. Therefore, investigators

[18] For a summary of amendments see NDA 20-386/SE1-028, Protocol No. 147, Appendix 3.3.3.

will need to acquire patient information such as full name, social security number, address, and contact number for a relative in order to access public records. Each subsidiary will work with the investigator to obtain this information through their respective governments as well.

4. Patients who have discontinued study drug may be restarted at any time on a case-by-case basis. Prior to reinitiating study therapy the investigator must receive approval from the sponsor if the time period for discontinuation of study drug has been >1 month. The investigator will call the sponsor with date of last dose of study therapy and reason for discontinuation to receive approval.

5. The Steering Committee has developed an algorithm for treatment of hypertension, especially for those patients with elevated systolic pressures. The algorithm is a recommended guideline, not a mandatory procedure, to assist the investigator in reaching the goal blood pressure of <140/90 mmHg.

Protocol Violations: Protocol violations were documented pre- and post randomization in 11 patients, 5 subjects received placebo and the remaining 6 were losartan-treated subjects. All randomized subjects were included in the intent to treat efficacy analysis dataset, whether or not a subject had a significant protocol violation. The type of protocol violation in each subject is provided in Table 1. In the losartan group one subject had insulin-dependent diabetes mellitus, three subjects had study therapy compliance <65%, and three subjects received ACE inhibitor or AIIA for >6 months during the study. Three subjects receiving placebo were also treated with an ACE inhibitor or AIIA for >6 months during the study, and two subjects had study therapy compliance <65%.

Table 1. Protocol Violation

Study Site	Allocation #	Treatment	Protocol Violation
147-004	2080	Losartan	Study therapy compliance <65%.
147-039	2390	Losartan	Patient with Insulin-Dependent Diabetes Mellitus.
147-199	3316	Losartan	Use of ACE inhibitor or AIIA >6 months during the study.
147-172	3936	Losartan	Study therapy compliance <65%.
147-163	4243	Losartan	Study therapy compliance <65% and ACEI/AIIA >6 months.
147-295	5056	Losartan	Use of ACE inhibitor or AIIA >6 months during the study.
147-101	1822	Placebo	Use of ACE inhibitor or AIIA >6 months during the study.
147-041	1872	Placebo	Use of ACE inhibitor or AIIA >6 months during the study.
147-371	2458	Placebo	Study therapy compliance <65%.
147-335	3067	Placebo	Use of ACE inhibitor or AIIA >6 months during the study.
147-290	5082	Placebo	Study therapy compliance <65%.

[Sponsor's analysis. Adapted from NDA 20-386/SE1-028, Protocol No. 147, Table 6.]

Unblinding: According to the sponsor, "a total of 6 patients were prematurely unblinded. Patient 2135 (Site 147-0013) experienced CHF, underwent a cardiac catheterization that revealed multiple coronary artery occlusions, and was unblinded at the request of the attending physician for medical management reasons. Patient 3329 (Site 147-0219) was inadvertently unblinded by the local monitor for regulatory adverse experience reporting purposes. This patient had been admitted with worsening renal function and uncontrolled hypertension. Patient 3334 (Site 147-0198) was admitted to the hospital with a myocardial infarction and left cardiac heart failure. The attending cardiologist requested to be unblinded for medical management reasons without the investigator's knowledge. Patient 3368 (Site 147-0218) was unblinded by the attending hospital physician when the patient was admitted with acute myocardial infarction and acute chronic renal failure. The unblinding occurred without the investigator's knowledge. Patient 3552 (Site 147-0193) was also unblinded for medical management reasons by the attending cardiologist. This patient had been admitted with angina pectoris, atrial fibrillation, and acute pulmonary edema. Patient 5024 (Site 147-0258) experienced unstable angina and acute heart failure and was unblinded at the primary investigator's request for medical management reasons."

Disposition of Subjects: 250 investigative sites in 29 countries from North and Latin America, Asia and Europe, randomized a total of 1513 subjects.

The number of patients randomized into the study by country and treatment group are summarized in Table 2. Of note, investigative sites in the United States enrolled forty-five percent of the patients.

Table 2. Number (%) of Patients Randomized by Country and Treatment Group.

Country	Losartan N=751 n	Placebo N=762 n	Total N=1513 n (%)
Argentina	9	8	17 (1.12)
Austria	8	7	15 (0.99)
Brazil	28	30	58 (3.83)
Canada	0	1	1 (0.06)
Chile	13	13	26 (1.71)
Costa Rica	17	16	33 (2.18)
Czech Republic	17	16	33 (2.18)
Denmark	8	8	16 (1.05)
France	5	7	12 (0.79)
Germany	6	6	12 (0.79)
Hong Kong	46	46	92 (6.08)
Hungary	5	5	10 (0.66)
Israel	19	18	37 (2.44)
Italy	13	13	26 (1.71)
Japan	44	52	96 (6.34)
Malaysia	11	10	21 (1.38)
Mexico	33	34	67 (4.42)
Netherlands	4	3	7 (0.46)
New Zealand	1	2	3 (0.19)
Peru	21	21	42 (2.77)
Portugal	5	5	10 (0.66)
Puerto Rico	2	3	5 (0.33)
Russian Federation	14	12	26 (1.71)
Singapore	5	6	11 (0.72)
Slovakia	1	1	2 (0.13)
Spain	36	31	67 (4.42)
United Kingdom	28	28	56 (3.70)
United States	336	345	681 (45.0)
Venezuela	16	15	31 (2.04)

[FDA's analysis. Source NDA 20-386/SE1-028, Protocol No. 147, Dataset: DEMOG.xpt.]

Table 3 summarizes the number of patients randomized into the study by region and treatment group. North America randomized 45.4% of the research subjects while Asia, Europe and Latin America randomized 17.0%, 19.5% and 18.1% of the subjects, respectively.

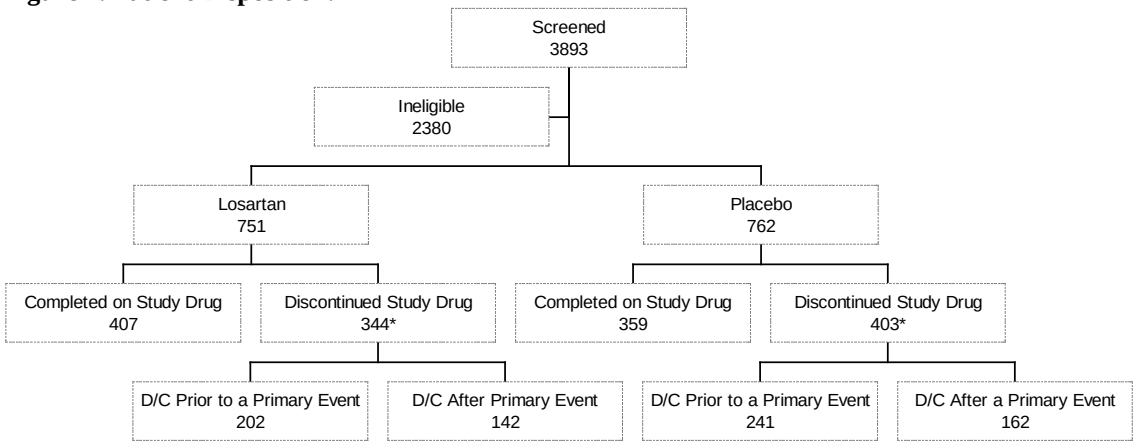
Table 3. Number (%) of Patients Randomized by Region and Treatment Group.

Region	Losartan N=751 n	Placebo N=762 n	Total N=1513 n (%)
Asia	125	132	257 (17.0)
Europe	151	144	295 (19.5)
Latin America	137	137	274 (18.1)
North America	338	349	687 (45.4)

[Sponsor's analysis. Adapted from NDA 20-386/SE1-028, Protocol No. 147, Table 5.]

As summarized in Figure 1, of the 751 and 762 patients randomized to losartan or placebo, 344 (45.8%) and 403 (52.9%) discontinued study therapy, respectively. This high rate of discontinuation is in accordance with the sponsor's prediction of 13% incidence per year. With respect to discontinuation from study drug prior to experiencing a primary endpoint, 202 (26.9%) losartan and 241 (31.6%) placebo treated patients discontinued study therapy.

Figure 1. Patient Disposition.



[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Response to FDA's request dated February 27, 2002. *Includes patients who died while on study drug.].

The protocol required that patients who discontinued study therapy be followed in the clinic every 3 months until the end of the study to allow for continued collection of primary and secondary endpoint information. Regular telephone contact was performed, if patients could no longer visit the clinic, in order to capture ESRD or death information; doubling of serum creatinine and cardiovascular outcomes could not be collected from patients in telephone follow-up. According to the sponsor no patient was lost to follow-up; outcomes of ESRD or death information were available in all randomized patients.

Table 4 displays the number of patients who were discontinued, for any reason (excluding those who died while on study therapy) and had a serum creatinine measurement done during the follow-up period. Approximately one-third of the patients had no measurement of serum creatinine and approximately two-thirds had at least one or more serum creatinine measurements after they were discontinued from study therapy.

Table 4. Summary of Serum Creatinine Measurements During the Off-therapy Follow-Up Period in Patients Discontinued for Any Reason

Treatment	Serum Creatinine Measurements	Count (%)
Losartan	0 Scr measurement	93 (33.3)
	1-3 Scr measurements	98 (35.1)
	>3 Scr measurements	88 (31.5)
	Total Patients	279
Placebo	0 Scr measurement	104 (31.2)
	1-3 Scr measurements	115 (34.5)
	>3 Scr measurements	114 (34.2)
	Total Patients	333

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Response to FDA's request dated February 27, 2002.]

Table 5 displays the number of patients who were discontinued prior to a primary endpoint and had a serum creatinine measurement done during the follow-up period. Again, approximately one-third of the patients had

no measurement of serum creatinine and approximately two-thirds had at least one or more serum creatinine measurements.

Table 5. Summary of Serum Creatinine Measurements During the Off-therapy Follow-up Period For Patients Who Discontinued Prior to Reaching the Endpoint

Treatment	Serum Creatinine Measurements	Count (%)
Losartan	0 Scr measurement	69 (34.5)
	1-3 Scr measurements	63 (31.5)
	>3 Scr measurements	68 (34.0)
	Total Patients	200
Placebo	0 Scr measurement	69 (28.8)
	1-3 Scr measurements	83 (34.6)
	>3 Scr measurements	88 (36.7)
	Total Patients	240

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Response to FDA's request dated February 27, 2002. Scr = Serum creatinine. 3 patients died while on therapy and are therefore not included in these counts, two on losartan (ANs 3905, 4591) and one on placebo (AN 3500).]

Table 6 shows the number (%) of patients randomized into the study and their disposition, i.e., whether they completed or discontinued the trial and the reason for discontinuation, by treatment group.[19] Noteworthy, overall 49.3% of the randomized subjects discontinued study drug, 45.8% of the subjects randomized to losartan and 52.8% subjects receiving placebo discontinued study drug prematurely. Slightly more patients receiving placebo (31.7%) than those treated with losartan (26.4%) were prematurely discontinued because of clinical adverse events. Laboratory adverse experiences were responsible for discontinuations in 2.6% and 2.1% of the patients receiving losartan and placebo, respectively.

Table 6. Discontinuation

	Losartan N=751 n (%)	Placebo N=762 n (%)	Total N=1513 n (%)
Completed Trial	407 (54.1)	359 (47.1)	766 (50.6)
Discontinued Trial	344 (45.8)	403 (52.8)	747 (49.3)
Clinical adverse experience	199 (26.4)	242 (31.7)	441 (29.1)
Laboratory adverse experience	20 (2.6)	16 (2.1)	36 (2.3)
Other reasonH	61 (8.1)	81 (10.6)	142 (9.3)
Patient moved	5 (0.6)	1 (0.1)	6 (0.3)
Patient withdrew consent	57 (7.5)	60 (7.8)	117 (7.7)
Protocol deviation	2 (0.3)	3 (0.3)	5 (0.3)
Patient was lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)

[Sponsor's analysis. Adapted from NDA 20-386/SE1-028, Protocol No. 147, Table 4. HIncludes miscellaneous reasons, e.g., patient unable to return for visits, or patient discontinued by personal physician.]

The number (%) of patients who withdrew from the trial, regardless causality, is presented by region in Table 7. It is worth mentioning that except for Asia, the discontinuation rates were similar between groups in the other regions. In Asia 26.4% of the subjects receiving losartan discontinued study drug prematurely versus 45.5% of the placebo-treated subjects.

[19] Table 1A (Appendix) summarizes reasons for discontinuation by region.

Table 7. All-Cause Discontinuation Summary by Region

Region	Losartan N/n (%)	Placebo N/n (%)	Total N/n (%)
Asia	125/33 (26.4)	132/60 (45.5)	257/93 (36.2)
Europe	151/69 (45.7)	144/71 (49.3)	295/140 (47.5)
Latin America	137/61 (44.5)	137/63 (46.0)	274/124 (45.3)
North America	338/181 (53.6)	349/209 (59.9)	687/390 (56.8)

[Sponsor's analysis. Adapted from NDA 20-386/SE1-028, Protocol No. 147, Table 5.]

Study Population: Table 8 provides a partial summary of patients' demographic and other baseline characteristics. A total of 1513 subjects were randomized into the clinical trial. The study population was predominantly composed of white (48.6%) males (63.2%) under the age of 65 years (66.4%) with a mean BMI of 29.7%. Noteworthy, even though normotensive as well as hypertensive patients could be enrolled into the trial, 96.6% of the randomized subjects were hypertensive at study entry. The mean baseline seated systolic and diastolic blood pressures were 152.5 mmHg and 82.4 mmHg, respectively.

The mean serum creatinine was 1.9 mg/dl and the mean proteinuria level (UA/Cr) was 1808 mg/gCr.

In ninety percent of the patients the duration of diabetes was ≥5 years, and 60.1% and 49.0% of the subjects had used insulin and oral anti-diabetics prior to study entry, respectively. In this regard, the mean glycosylated hemoglobin ($HbA1_c$) level for the entire population was 8.5%.

A history of cardiovascular disease, i.e., prior angina was present in only 9.3% of the randomized subjects, and 12.8% had a history of prior myocardial infarction. Besides a history of nephropathy, which was one of the study entry criteria, retinopathy (63.9%) and neuropathy (50.0%) were among the most common diabetic-related conditions reported at randomization. Only, 8.9% of the subjects did have a history of prior amputation.

While 48.7% of the subjects received ACE inhibitors prior to randomization only 3.2% of the patients reported prior use of AII receptor antagonists. Most commonly use antihypertensive drugs reported by the subjects were calcium channel blockers (71.2%) and diuretics (58.0%), whereas beta-blockers use was reported by 24.1% of the patients.

Thirty three percent and 36.3% of the patients reported use of aspirin and lipid-lowering agents prior to randomization, respectively.

Overall, based on comparison of the means, there were no significant differences/imbalances between the treatment groups in baseline demographic characteristics, blood pressure, prior therapies, and laboratory measures (Table 8).

Table 8. Patient Demographic and Other Baseline Characteristics

Variable		Losartan N=751 n (%)	Placebo N=762 n (%)	Total N=1513 n (%)
Gender:	Female	289 (38.5%)	268 (35.2%)	557 (36.8%)
	Male	462 (61.5%)	494 (64.8%)	956 (63.2%)
Age (yr)H:	<65	503 (66.9%)	502 (65.8%)	1005 (66.4%)
	≥65	248 (33.0%)	260 (34.1%)	508 (33.5%)
Race:	Asian	117 (15.6%)	135 (17.7%)	252 (16.7%)
	Black	125 (16.6%)	105 (13.8%)	230 (15.2%)
	Hispanic	140 (18.6%)	137 (18.0%)	277 (18.3%)
	Other	11 (1.5%)	8 (1.0%)	19 (1.3%)
	White	358 (47.7%)	377 (49.5%)	735 (48.6%)
Hypertensive*		720 (95.8%)	743 (97.5%)	1463 (96.6%)
Body Mass Index (Mean (SD), kg/M^2)		30.0 (6.4)	29.4 (6.2)	29.7 (6.3)

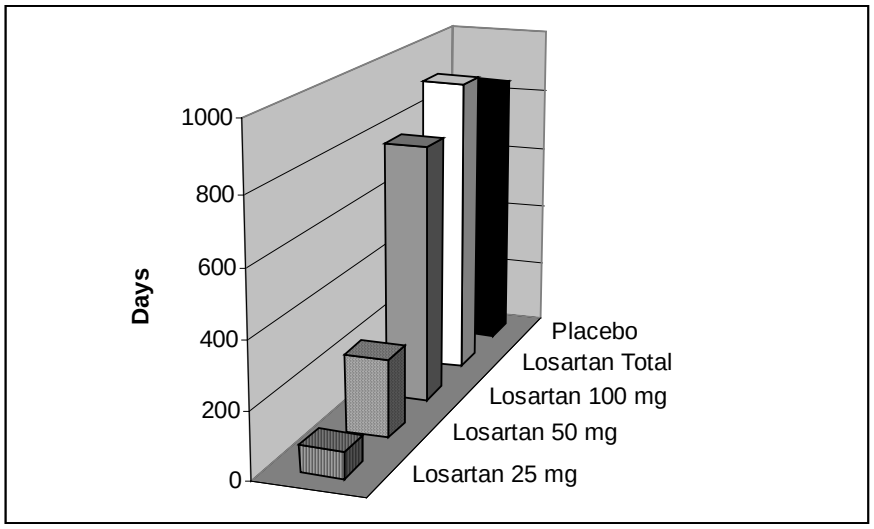
Table 8. Cont'd

Serum Creatinine (Mean (SD), mg/dL)H	1.9 (0.5)	1.9 (0.5)	1.9 (0.5)
Proteinuria (Mean (SD),UA/Cr in mg/g)	1873 (1831)	1743 (1543)	1808 (1693)
HbA1c (Mean (SD) %)	8.5 (1.7)	8.4 (1.6)	8.5 (1.6)
Sitting Systolic BP (Mean (SD)mm Hg)	151.8 (18.7)	153.2 (19.9)	152.5 (19.3)
Sitting Diastolic BP (Mean (SD)mm Hg)	82.4 (10.3)	82.4 (10.6)	82.4 (10.4)
Duration of Diabetes ≥5 yr	676 (90.0%)	686 (90.0%)	1362 (90.0%)
Prior Amputation	65 (8.7%)	70 (9.2%)	135 (8.9%)
Prior Angina	66 (8.8%)	75 (9.8%)	141 (9.3%)
Prior MI	88 (11.7%)	105 (13.8%)	193 (12.8%)
Prior Neuropathy	377 (50.2%)	380 (49.4%)	757 (50.0%)
Prior Retinopathy	495 (65.9%)	472 (61.9%)	967 (63.9%)
Insulin Use	461 (61.4%)	449 (58.9%)	910 (60.1%)
Oral Antidiabetics Use	361 (48.1%)	381 (50.0%)	742 (49.0%)
Prior ACE Inhibitor Use	376 (50.1%)	361 (47.4%)	737 (48.7%)
Prior AIIA Use	29 (3.9%)	20 (2.6%)	49 (3.2%)
Beta Blocker Use	137 (18.2%)	140 (18.4%)	277 (18.3%)
Calcium Channel Blocker (CCB) Use	532 (70.8%)	546 (71.7%)	1078 (71.2%)
Diuretic Use	442 (58.9%)	436 (57.2%)	878 (58.0%)
Aspirin Use	255 (34.0%)	244 (32.0%)	499 (33.0%)
Lipid-Lowering Agents Use	274 (36.5%)	275 (36.1%)	549 (36.3%)

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 7. *Hypertensive: on antihypertensive drugs or SiDBP >90 mmHg and SiSBP >140 mmHg. HSome patients who did not meet entry criteria for serum creatinine, or age were randomized. SD denotes standard deviation.]

Extent of Exposure: The study lasted 3.4 years. The mean duration of exposure to placebo or losartan by daily dose is depicted in Figure 2. Overall, patients in the losartan group (regardless of dosage), as compared with placebo-treated patients, had a slightly longer mean duration of exposure to study drug, 913.4 days *vs.* 845.3 days, respectively.

Figure 2. Mean Duration of Drug Exposure by Daily Dose.



[Sponsor's analysis. Adapted from: NDA 20-386/SE1-028, Protocol No. 147, Table 45.]

Table 9 shows the extent of exposure to losartan and placebo and summarizes the number and percent of patients who took 25, 50, 100 mg of losartan daily more than 50% of the time during double-blind treatment.

Table 9. Extent of Exposure

Time	Losartan daily Dose				Placebo
	25 mg n(%)	50 mg n(%)	100 mg n(%)	Total N	N
Day 1+	57 (7.6%)	693 (92.3%)	1 (0.1%)	751	762
Week 1	15 (2%)	699 (93.1%)	37 (4.9%)	751	762
Month 1	8 (1.1%)	379 (50.9%)	358 (48.1%)	745	750
Month 3	6 (0.8%)	252 (34.4%)	475 (64.8%)	733	731
Month 6	6 (0.9%)	195 (27.7%)	502 (71.4%)	703	690
Month 9	5 (0.7%)	174 (25.7%)	498 (73.6%)	677	650
Month 12	3 (0.5%)	146 (22.7%)	495 (76.9%)	644	618
Month 15	4 (0.7%)	119 (19.5%)	487 (79.8%)	610	579
Month 18	5 (0.9%)	112 (19.0%)	471 (80.1%)	588	557
Month 21	4 (0.7%)	104 (18.8%)	446 (80.5%)	554	529
Month 24	4 (0.8%)	88 (16.5%)	440 (82.7%)	532	502
Month 27	4 (0.8%)	74 (14.6%)	430 (84.6%)	508	472
Month 30	5 (1 %)	63 (12.9%)	421 (86.1 %)	489	452
Month 33	2 (0.5%)	54 (12.4%)	378 (87.1%)	434	395
Month 36	2 (0.6%)	47 (13.5%)	298 (85.9%)	347	317
Month 39	1 (0.3%)	34 (11.8%)	253 (87.8%)	288	251
Month 42	1 (0.5%)	26 (12.7%)	178 (86.8%)	205	176
Month 45	0 (0.0%)	18 (11.3%)	142 (88.8%)	160	130
Month 48	0 (0.0%)	11 (I 1.5%)	85 (88.5%)	96	71
Month 51	0 (0.0%)	4 (10.3%)	35 (89.7%)	39	24
Month 54	0 (0.0%)	1 (33.3%)	2 (66.7%)	3	2
Range (Days on Rx)	1 to 912	1 to 1595	1 to 1589	3 to 1631	1 to 1631
Mean Duration	81.4	236.4	784.8	913.4	845.3

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 45. Dosages not planned in protocol: Allocation number (AN) 2018 took 200 mg/day for 57 days, AN 2437 took 200 mg/day for 26 days, AN 3203 took 75 mg/day for 86 days, AN 3279 took 150 mg/day for I day, AN 3474 took 200 mg/day for 8 days, and AN 4213 took 200 mg/day for 25 days.]

Daily dose of study drug: Table 10 shows the number and percentage of patients who took the designated dose of losartan more than 50% of the time during double-blind treatment. The percentage of patients who took the designated daily dose of losartan more than 50% of the time is as follows: 1.6% took 25 mg, 26.6% took 50 mg and 71.8% took 100 mg.

Table 10. Number (%) of Patients Who Took the Designated Dose of Losartan More Than 50% of the Time

Losartan daily Dose			
25 mg n(%)	50 mg n(%)	100 mg n(%)	Total N
12 (1.6%)	200 (26.6%)	539 (71.8%)	745

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 46].

Treatment Compliance: One thousand four hundred ninety (98.4%) patients were compliant.[20] Table 11 displays the percentage of patients who were compliant with taking their study drug on a daily basis more than 80% of the time while they were in the double-blind treatment period, that is, between randomization and permanent study drug discontinuation.

Table 11. Study Therapy Compliance

Treatment	Overall	Compliance >80% of the double-blind period	
	N	N	%
Losartan	751	739	98.4
Placebo	762	751	98.6

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Response to FDA's request dated February 27, 2002.].

[20] Sponsor response to FDA's request dated February 21, 2002.

***Concomitant Medications*:** Table 12 displays the number (%) of patients receiving specific concomitant medications for more than 14 days during double-blind treatment. As expected the incidence of use of other antihypertensives, i.e., Alpha blockers, Beta blockers, Calcium channel blockers, and Centrally acting agents, was higher in the placebo group than in the losartan group. On the other hand, the use of medications other than antihypertensives was similar between the groups.

Table 12. Number (%) of Patients Receiving Specific Concomitant Medications During Double-Blind Treatment (>14 Days).

Medication	Losartan N=751 n (%)	Placebo N=762 n (%)
ACEI or AIIA	52 (6.9)	66 (8.7)
Alpha blocker	314 (41.8)	360 (47.2)
Alpha glucosidase inhibitors	50 (6.7)	51 (6.7)
Beta blocker	267 (35.6)	288 (37.8)
Biguanides	121 (16.1)	110 (14.4)
Biguanides and sulfonamides in combination	15 (2.0)	22 (2.9)
Bile acid sequestrants	2 (0.3)	6 (0.8)
CCB	608 (81.0)	633 (83.1)
Centrally acting agents	144 (19.2)	171 (22.4)
Cholesterol and triglyceride reducer	399 (53.1)	416 (54.6)
Dihydropyridines	481 (64.0)	509 (66.8)
Diuretics	636 (84.7)	646 (84.8)
Erythropoeitin	58 (7.7)	61 (8.0)
Fibrates	115 (15.3)	120 (15.7)
HMB CoA reductase inhibitors	342 (45.5)	352 (46.2)
Insulin	514 (68.4)	507 (66.5)
Nicotinic acid derivatives	6 (0.8)	9 (1.2)
Non-dihydropyridines	219 (29.2)	202 (26.5)
Oral hypoglycemic	407 (54.2)	419 (55.0)
Other glucose-lowering drugs	7 (0.9)	11 (1.4)
Serum lipid-reducing agent	399 (53.1)	416 (54.6)
Sulfonamides, urea derivatives	310 (41.3)	343 (45.0)
Thiazolidinediones	116 (15.4)	92 (12.1)

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 48.]

Efficacy Results: The primary endpoint was a composite endpoint, defined as time to doubling of serum creatinine, end-stage renal disease (ESRD), or death, whichever occur first. The results of the intent-to-treat analysis[21] for the primary composite endpoint are summarized in Table 13. Losartan administration had a modest treatment benefit (over placebo) resulting in an estimated risk reduction of 16.1% (p=0.022, 95.2% confidence interval 2.3%, 27.9%). The primary endpoint was reached in 327 (43.5%) of the subjects receiving losartan *vs.* 359 (47.1%) of the placebo-treated subjects, the difference in the number of events between the groups is thirty-two.

[21] This analysis included all randomized patients according to the treatment to which they were randomly assigned, regardless of any protocol violation, and also regardless of whether they continued to take the assigned study medication during the trial. Cox model using geographical region as covariate and baseline proteinuria as a stratification variable.

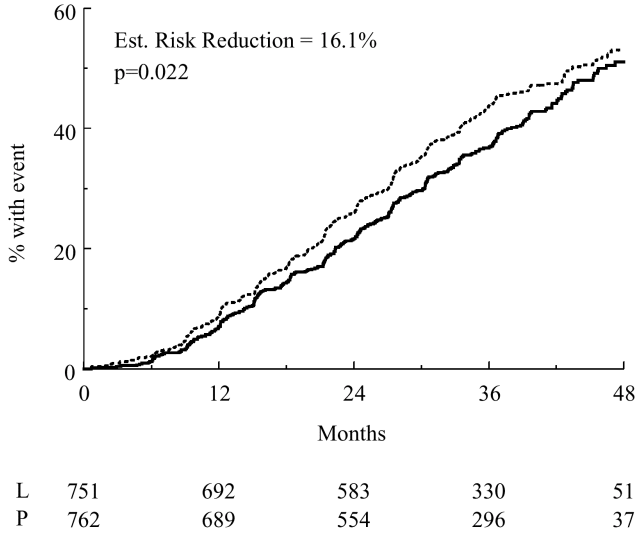
Table 13. Primary Composite Endpoint of Doubling Serum Creatinine, End-Stage Renal Disease, or Death. Intent-to-Treat Analysis

Losartan n/N (%)	Placebo n/N (%)	Est. Risk Reduction	95.2% Confidence Interval	p-Value
327/751 (43.5)	359/762 (47.1)	16.1%	(2.3%, 27.9%)	0.022

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 8. The status of all patients as of the study termination date of 10-Feb-2001, in terms of dialysis, transplantation, or death, determined. Est. indicates estimation using a proportional hazards regression model with adjustments for region and proteinuria stratum.]

Cumulative event rates for the primary composite endpoint of doubling of serum creatinine, end-stage renal disease or death for the intent-to-teat analysis are depicted in Figure 3 based on the Kaplan-Meier curve. The losartan group had discernible lower event rates than the placebo group approximately nine months after treatment started.

Figure 3. Kaplan-Meier Curves for the Primary Composite Endpoint of Doubling Serum Creatinine, End-Stage Renal Disease, or Death. Intent-to-Treat Analysis



[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Figure 2. The numbers below the graphic the number of patients at risk at various time points.]

Table 14 shows the results of the following analyses: first occurring event and total incidence for the individual components of the primary composite endpoint. The treatment benefit provided by losartan was due entirely on its effect on time to doubling of serum creatinine. The risk of the component endpoint of doubling of serum creatinine was reduced by 25.3% (p=0.006, 95.2% confidence interval 0.61, 0.92) in losartan-treated subjects. Losartan treatment had no effect on time to ESRD (p=0.66) or death (p=0.91).

Relevant to the interpretation of the study are the results of the analysis of the total incidence for the morbid and mortal components of the primary composite endpoint (Table 14). Albeit losartan treatment did not affect mortality (p=0.884, 95.2% confidence interval 0.81, 1.27), losartan-treated patients had significantly fewer ESRD events as compared with those subjects in the placebo group, 147 *vs.* 194, respectively (p=0.002, risk reduction of 28.6%, 95.2% confidence interval 0.57, 0.89). The difference in the number of ESRD events between the groups is forty-seven.

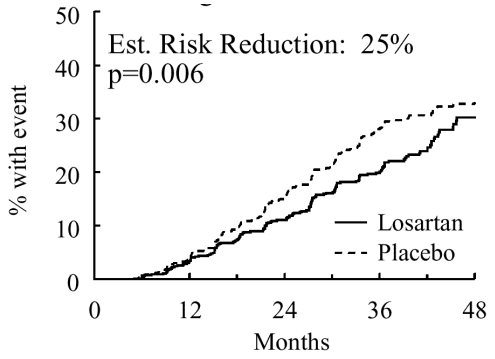
Table 14. Individual Components of the Primary Composite Endpoint: Doubling Serum Creatinine, End-Stage Renal Disease, or Death. Intent-to-Treat Analysis

Component	Losartan N=751 n (%)	Placebo N=762 n (%)	Est. Risk Reduction	Hazard Ratio (95.2 CI)	p-Value
Breakdown of the First Occurring Component of Primary Event:					
Doubling of sCreatinine	162 (21.6)	198 (26.0)	25.3%	0.75 (0.61, 0.92)	0.006
ESRD	64 (8.5)	65 (8.5)	7.0%	0.93 (0.65, 1.31)	0.66
Death	101 (13.4)	96 (12.6)	2.0%	0.98 (0.74, 1.30)	0.91
Total (Cumulative) Incidence of Each Component of Primary Endpoint:					
Doubling of sCreatinine	162 (21.6)	198 (26.0)	25.3%	0.75 (0.61, 0.92)	0.006
ESRD	147 (19.6)	194 (25.5)	28.6%	0.71 (0.57, 0.89)	0.002
Death	158 (21.0)	155 (20.3)	-1.7%	1.02 (0.81, 1.27)	0.884

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 9, and Response to FDA request dated January 30, 2002. sCreatinine = serum creatinine. Confirmed by FDA's analysis, Dr. Hsien Ming J Hung (HFD-710).]

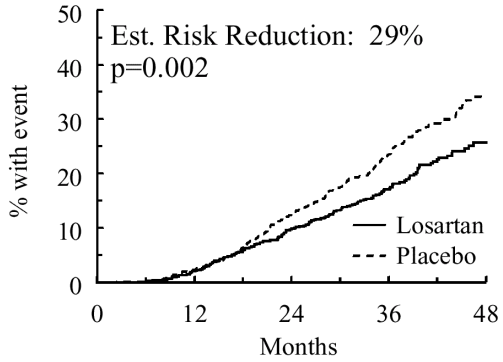
Figures 4 and 5 depict the Kaplan-Meier curves for the unadjusted cumulative event rates for doubling of serum creatinine and ESRD, respectively. Approximately after 12 and 18 months of therapy with study drug the losartan curve separated from the placebo curve for both doubling of serum creatinine and ESRD, respectively.

Figure 4. Kaplan-Meier Curves for the Doubling Serum Creatinine Component of the Primary Composite Endpoint. Intent-to-Treat Analysis



[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Figure 3.]

Figure 5. Kaplan-Meier Curves for the ESRD Component of the Primary Composite Endpoint. Intent-to-Treat Analysis



[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Figure 3.]

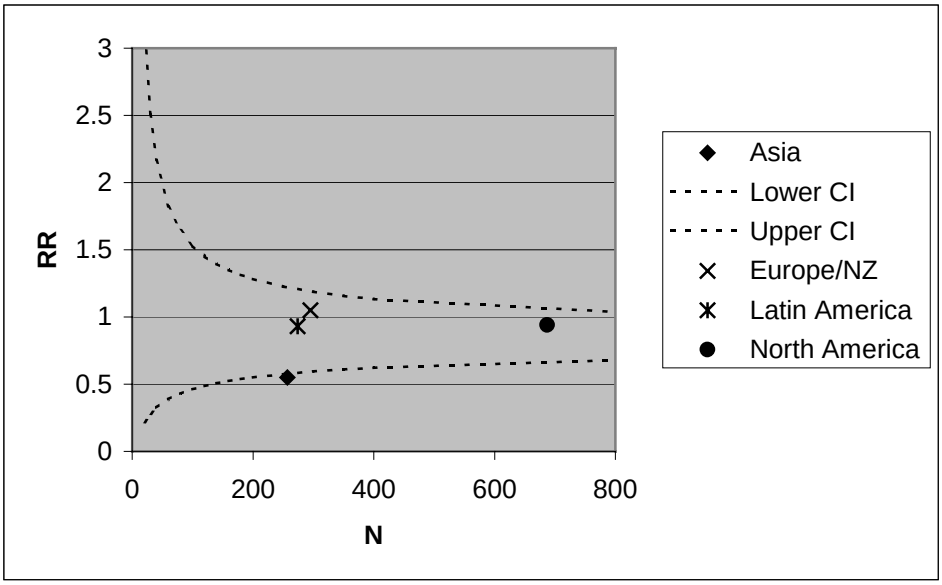
The primary composite endpoint was also analyzed by region (n=4) and by country (n=28) (Table 15 and Figure 6, and Table 16 and Figure 7, respectively). The plots depicted in Figures 6 and 7 show relative risk (losartan over placebo) by number of subjects randomized in the given region or country, respectively. It is worth mentioning that these represent retrospective analyses. Asia was the region in which losartan had the largest treatment effect, with an estimated risk reduction of 45% *vs.* an overall risk reduction of 16.1%. Losartan treatment had a small effect in Latin and North America and no effect in Europe. However as can be appreciated from Figure 6 the point estimate of the effect from Asia overlap with the 95% lower confidence limit; indicating that Asia is not a "true" outlier and thus that there is not "significant" regional heterogeneity.

Table 15. Primary Composite Endpoint (Doubling Serum Creatinine, ESRD, Death) by Region

Region	Losartan	Placebo	Hazard ratio (95% CI)
All regions	**327/751 (43.5%)**	**359/762 (47.1%)**	**0.84 (0.72, 0.98)**
Asia	49/125 (39.2%)	78/132 (59.1%)	0.55 (0.39, 0.79)
Europe	58/151 (38.4%)	51/144 (35.4%)	1.05 (0.72, 1.53)
Latin America	78/137 (56.9%)	80/137 (58.4%)	0.93 (0.68, 1.27)
North America	142/338 (42.0%)	150/349 (43.0%)	0.94 (0.75, 1.19)

[FDA's analysis by Dr. Hsien Ming J Hung (HFD-710).]

Figure 6. Relative Risk of Primary Composite Endpoint by Region.[22]



[FDA's analysis by Dr. Juan C Pelayo (HFD-110) based on data analysis by Dr. Hsien Ming J Hung (HFD-710) and analysis/graphing by Dr. Norman Stockbridge (HFD-110). CI = confidence interval.]

The results of the analysis of the primary composite endpoint by country are summarized in Table 16, and depicted in Figure 7. Examination of the plot in Figure 7 indicates that Israel is the only country which had the largest relative risk reduction of 78% (Hazard ratio 0.22, 95% confidence interval 0.07, 0.70), which fell outside the 95% confidence limits and thus it could be considered an "outlier".

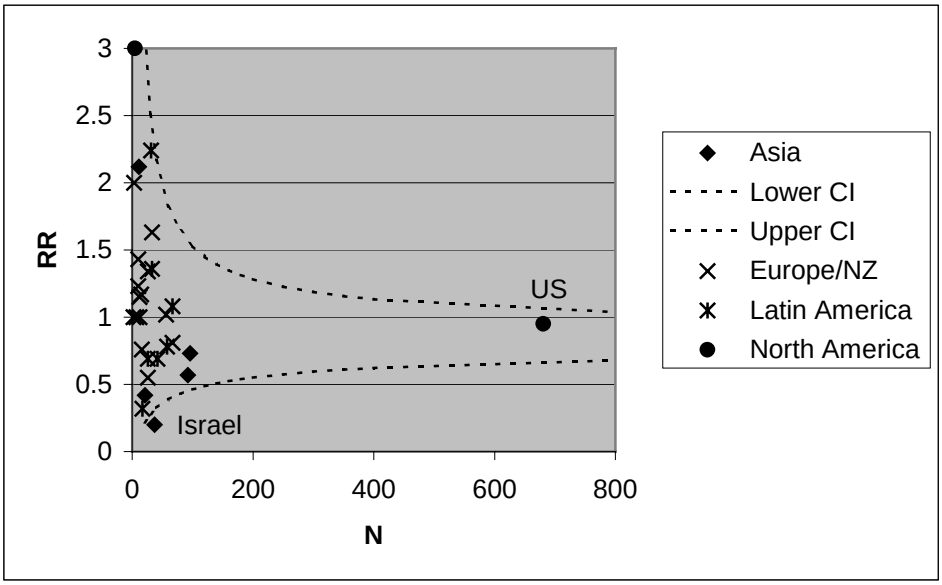
[22] Relative risk of primary endpoint events was calculated by Dr. Hung. The bounding curves show the overall 95% confidence limits log-transformed and scaled by the square root of N, as calculated by Dr. Stockbridge.

Table 16. Primary Composite Endpoint (Doubling Serum Creatinine, ESRD, Death) by Country

Region	Country	Losartan	Placebo	Hazard ratio (95% CI)
All regions		**327/751 (43.5%)**	**359/762 (47.1%)**	**0.84 (0.72, 0.98)**
Asia	Hong Kong	19/46 (41.3%)	27/46 (58.7%)	0.57 (0.32, 1.04)
	Israel	4/19 (21.1%)	12/18 (66.7%)	0.22 (0.07, 0.70)
	Japan	22/44 (50.0%)	34/52 (65.4%)	0.73 (0.43, 1.26)
	Malaysia	2/11 (18.2%)	4/10 (40.0%)	0.42 (0.08, 2.31)
	Singapore	2/5 (40.0%)	1/6 (16.7%)	2.12 (0.19, 23.51)
Europe	Austria	5/8 (62.5%)	4/7 (57.1%)	1.17 (0.31, 4.38)
	Czech Republic	9/17 (52.9%)	6/16 (37.5%)	1.63(0.58, 4.59)
	Denmark	3/8 (37.5%)	3/8 (37.5%)	0.76 (0.15, 3.83)
	France	5/5 (100%)	7/7 (100%)	1
	Germany	3/6 (50.0%)	2/6 (33.3%)	1.15 (0.19, 6.97)
	Hungary	3/5 (60.0%)	2/5 (40.0%)	1.43 (0.24, 8.61)
	Italy	2/13 (15.4%)	3/13 (23.1%)	0.55 (0.09, 3.33)
	Netherlands	4/4 (100%)	3/3 (100%)	1
	New Zealand	1/1 (100%)	1/2 (50.0%)	2
	Portugal	3/5 (60.0%)	2/5 (40.0%)	1.23 (0.20, 7.40)
	Russian Federation	6/14 (42.9%)	4/12 (33.3%)	1.34 (0.38, 4.77)
	Slovakia	1/1 (100%)	1/1 (100%)	1
	Spain	14/36 (38.9%)	14/31 (45.2%)	0.81 (0.38, 1.69)
	United Kingdom	10/28 (35.7%)	10/28 (35.7%)	1.02 (0.42, 2.45)
Latin America	Argentina	2/9 (22.2%)	5/8 (62.5%)	0.32 (0.06, 1.65)
	Brazil	17/28 (60.7%)	20/30 (66.7%)	0.78 (0.41, 1.49)
	Chile	7/13 (53.8%)	8/13 (61.5%)	0.69 (0.25, 1.91)
	Costa Rica	12/17 (70.6%)	8/16 (50.0%)	1.36 (0.55, 3.34)
	Mexico	19/33 (57.6%)	18/34 (52.9%)	1.08 (0.57, 2.07)
	Peru	10/21 (47.6%)	13/21 (61.9%)	0.69 (0.30, 1.58)
	Venezuela	11/16 (68.8%)	8/15 (53.3%)	2.24 (0.82, 6.08)
North America	Canada	.	1/1 (100%)	.
	Puerto Rico	2/2 (100%)	1/3 (33.3%)	3
	United States	142/336 (42.3%)	148/345 (42.9%)	0.95 (0.76, 1.20)

[FDA's analysis by Dr. Hsien Ming J Hung (HFD-710).]

Figure 7. Relative Risk of Primary Composite Endpoint by Country.



[FDA's analysis by Dr. Norman Stockbridge (HFD-110) based on data analysis by Dr. Hsien Ming J Hung (HFD-710).]

The results of the subgroup analysis of the primary endpoint by demographic variables or baseline factors are shown in Table 17. The retrospective nature of the analysis in addition to the small number of patients in each category per group precludes a valid commentary on the findings.

Table 17. Subgroup Analysis of Primary Composite Endpoint. Intent-to-Treat Analysis

	Losartan (N=751)	**Placebo (N=762)**	**Hazard ratio (95% CI)**
Female	138 / 289 (47.8 %)	145 / 268 (54.1 %)	0.80 (0.64 , 1.01)
Male	189 / 462 (40.9 %)	214 / 494 (43.3 %)	0.90 (0.74 , 1.09)
Age			
< 65 yrs	222 / 503 (44.1 %)	246 / 502 (49.0 %)	0.83 (0.69 , 1.00)
≥ 65 yrs	105 / 248 (42.3 %)	113 / 260 (43.5 %)	0.95 (0.73 , 1.23)
Asian	49 / 117 (41.9 %)	74 / 135 (54.8 %)	0.69 (0.48 , 0.99)
Hispanic	77 / 140 (55.0 %)	74 / 137 (54.0 %)	1.01 (0.74 , 1.39)
black	50 / 125 (40.0 %)	41 / 105 (39.0 %)	0.97 (0.64 , 1.47)
white	145 / 358 (40.5 %)	163 / 377 (43.2 %)	0.87 (0.69 , 1.09)
Proteinuria			
< 2000 mg/g	150 / 501 (29.9 %)	161 / 511 (31.5 %)	0.91 (0.73, 1.14)
≥ 2000 mg/g	177 / 250 (70.8 %)	198 / 251 (78.9 %)	0.78 (0.64, 0.96)
BMI			
< 30 kg/m2	195 / 437 (44.6 %)	226 / 471 (48.0 %)	0.87 (0.72 , 1.06)
≥ 30 kg/m2	132 / 314 (42.0 %)	133 / 291 (45.7 %)	0.88 (0.69 , 1.11)
Duration of hypertension			
< 10 yrs	178 / 387 (46.0 %)	204 / 409 (49.9 %)	0.88 (0.72 , 1.08)
≥ 10 yrs	149 / 364 (40.9 %)	155 / 353 (43.9 %)	0.86 (0.69 , 1.08)
Total Cholesterol			
< 240 mg/dL	187 / 496 (37.7 %)	205 / 489 (41.9 %)	0.84 (0.69 , 1.03)
≥ 240 mg/dL	140 / 255 (54.9 %)	154 / 273 (56.4 %)	0.93 (0.74 , 1.17)

Table 17. Cont'd

Serum Creatinine			
< 2 mg/dL	174 / 482 (36.1 %)	173 / 483 (35.8 %)	0.97 (0.78 , 1.20)
≥ 2 mg/dL	153 / 269 (56.9 %)	186 / 279 (66.7 %)	0.77 (0.62 , 0.95)
Serum Albumin			
< 3.6 mg/dL	143 / 207 (69.1 %)	145 / 202 (71.8 %)	0.87 (0.69 , 1.10)
≥ 3.6 mg/dL	184 / 544 (33.8 %)	214 / 560 (38.2 %)	0.84 (0.69 , 1.02)
Serum Uric Acid			
< 7 mg/dL	197 / 459 (42.9 %)	203 / 448 (45.3 %)	0.90 (0.74 , 1.09)
≥ 7 mg/dL	130 / 292 (44.5 %)	156 / 314 (49.7 %)	0.83 (0.66 , 1.05)
HbA1c			
< 10%	5 / 9 (55.6 %)	2 / 8 (25.0 %)	2.73 (0.53 , 14.1)
≥ 10%	322 / 742 (43.4 %)	357 / 754 (47.3 %)	0.86 (0.74 , 1.00)
Hemoglobin			
< 12 mg/dL	163 / 315 (51.7 %)	178 / 310 (57.4 %)	0.81 (0.66 , 1.01)
≥ 12 mg/dL	164 / 436 (37.6 %)	181 / 452 (40.0 %)	0.90 (0.73 , 1.11)
Nonsmoker	69 / 147 (46.9 %)	61 / 130 (46.9 %)	0.98 (0.70 , 1.39)
Smoker	258 / 604 (42.7 %)	298 / 632 (47.2 %)	0.84 (0.71 , 0.99)
Sitting SBP			
< 140 mmHg	60 / 191 (31.4 %)	66 / 187 (35.3 %)	0.86 (0.61 , 1.22)
≥ 140 mmHg	267 / 560 (47.7 %)	293 / 575 (51.0 %)	0.87 (0.74 , 1.03)
Insulin Use			
No	113 / 290 (39.0 %)	128 / 313 (40.9 %)	0.92 (0.71 , 1.18)
Yes	214 / 461 (46.4 %)	231 / 449 (51.4 %)	0.83 (0.69 , 1.00)
Dihydropyridine			
No	128 / 345 (37.1 %)	148 / 351 (42.2 %)	0.84 (0.66 , 1.06)
Yes	199 / 406 (49.0 %)	211 / 411 (51.3 %)	0.89 (0.74 , 1.08)
ACEI or AIIA Use			
No	146 / 351 (41.6 %)	180 / 386 (46.6 %)	0.85 (0.68 , 1.06)
Yes	181 / 400 (45.3 %)	179 / 376 (47.6 %)	0.88 (0.72 , 1.08)
Beta Blocker Use			
No	265 / 614 (43.2 %)	298 / 622 (47.9 %)	0.84 (0.72 , 1.00)
Yes	62 / 137 (45.3 %)	61 / 140 (43.6 %)	0.99 (0.69 , 1.41)
Calcium Blocker Use			
No	82 / 219 (37.4 %)	89 / 216 (41.2 %)	0.84 (0.62 , 1.14)
Yes	245 / 532 (46.1 %)	270 / 546 (49.5 %)	0.88 (0.74 , 1.05)

[FDA's analysis by Dr. Hsien Ming J Hung (HFD-710).]

The secondary efficacy endpoint was a composite of cardiovascular morbidity/mortality, pre-specified as the time to first event of myocardial infarction, stroke, hospitalization for heart failure or unstable angina, coronary or peripheral revascularization, or cardiovascular deaths. The results of the intent-to-treat analysis of the secondary composite endpoint are summarized in Table 18. The estimated risk reduction (losartan *vs.* placebo) was 9.6% (95% confidence interval -7.5%, 24.0%, p=0.253). Thus losartan administration failed to effect a treatment benefit on cardiovascular morbidity and mortality. It is worth mentioning that the study was not powered to evaluate the effect of losartan on cardiovascular morbidity/mortality.

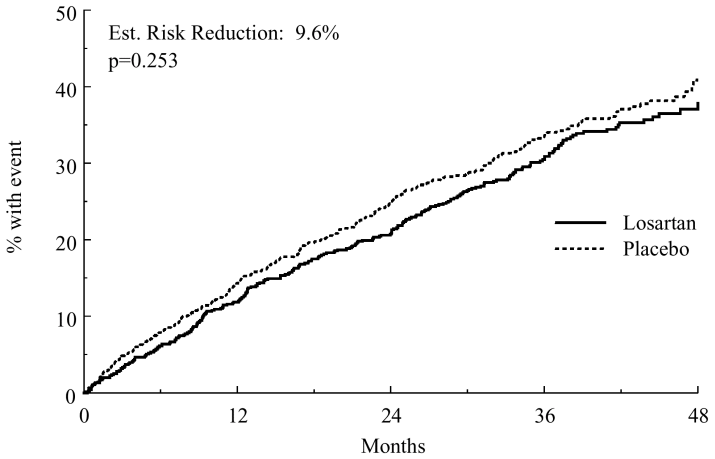
Table 18. Secondary Composite Endpoint of Cardiovascular Morbidity/Mortality. Intent-to-Treat Analysis

Losartan n/N (%)	Placebo n/N (%)	Est. Risk Reduction	95% Confidence Interval	p-Value
247/751 (32.9)	268/762 (35.2)	9.6%	(-7.5%, 24.0%)	0.253

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 10. The status of all patients as of the study termination date of 10-Feb-2001, in terms of dialysis, transplantation, or death, determined.]

Figure 8 depicts the Kaplan-Meier curve for the composite of cardiovascular morbidity/mortality.

Figure 8. Kaplan-Meier Curves for the Secondary Composite Endpoint of Cardiovascular Morbidity/Mortality. Intent-to-Treat Analysis



[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Figure 4.]

The cumulative incidence of each component of the secondary composite efficacy endpoint of cardiovascular morbidity/mortality that is myocardial infarction, stroke, hospitalization for heart failure or unstable angina, coronary or peripheral revascularization, or cardiovascular deaths, is summarized in Table 19. Except for hospitalization for heart failure there were no significant differences on the cardiovascular components. Losartan reduced the risk for hospitalization for heart failure by 31.6% (89 patients with losartan *vs.* 126 with placebo; hazard ratio 0.68, p=0.006).[23]

Table 19. Total Incidence of Components of Secondary Endpoint. Intent-to-Treat Analysis

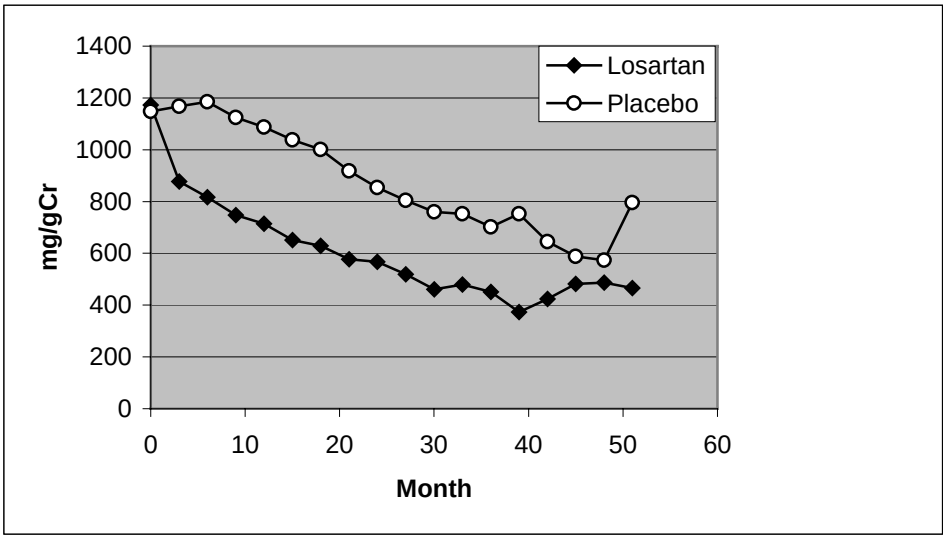
	Losartan (N=751)	Placebo (N=762)	Hazard ratio (95% CI)	p-Value
Hosp. for HF	89 (11.9%)	126 (16.5%)	0.68 (0.52, 0.90)	0.006
MI	50 (6.7%)	68 (8.9%)	0.72 (0.50, 1.04)	0.079
Stroke	47 (6.3%)	50 (6.6%)	0.85 (0.64, 1.41)	0.78
Cardiovascular death	90 (12.0%)	79 (10.4%)	1.12 (0.83, 1.52)	0.45
Revascularization	69 (9.2%)	60 (7.9%)	1.19 (0.84, 1.68)	0.34
Hosp. for Unstable angina	42 (5.6%)	41 (5.4%)	1.03 (0.67, 1.59)	0.89

[FDA's analysis by Dr. Hsien Ming J Hung (HFD-710). Hosp. = Hospitalization.]

Secondary efficacy analyses also included the assessment of changes in proteinuria and progression of renal disease.[24] Proteinuria was measured as the ratio of urinary albumin to creatinine from a first morning urine sample analyzed by the central laboratory. Figure 9 and Table 20 depict the mean changes over time in proteinuria (mg/gCr) and p-values resulting from the comparison between the groups. The rate of urinary protein excretion fell over time in both groups, however losartan treatment reduced proteinuria to a greater extent than placebo, on average 33% (Table 20). This effect was statistically significant at month 3 through month 42.

[23] p-Value adjusted for region and stratum.
[24] Amendment 147-03 contained the following change: A new secondary hypothesis and objective is added to assess the effect of losartan on progression of renal disease as measured by the reciprocal of serum creatinine.

Figure 9. Proteinuria (Geometric mean, mg/gCr) over Time. Intent-to-Treat Analysis



[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 79.]

Table 20. Summary of Proteinuria (Geometric mean, mg/gCr) over Time. Intent-to-Treat Analysis

Month	Losartan		Placebo		GM Ratio	p-Value
	n	GM	n	GM		
0	751	1172.52	762	1148.50	1.02	0.69
3	694	877.05	689	1167.51	0.75	<0.001
6	679	816.67	672	1185.20	0.69	<0.001
9	659	747.04	634	1124.05	0.66	<0.001
12	636	713.85	598	1086.89	0.66	<0.001
15	604	651.25	580	1037.92	0.63	<0.001
18	582	628.99	548	1000.71	0.63	<0.001
21	554	576.56	520	918.40	0.63	<0.001
24	517	566.74	500	854.42	0.66	<0.001
27	503	518.54	463	804.46	0.64	<0.001
30	444	460.34	418	760.14	0.61	<0.001
33	385	479.79	340	752.77	0.64	<0.001
36	306	450.99	269	701.56	0.64	<0.001
39	237	373.43	196	753.10	0.50	<0.001
42	176	423.86	137	644.84	0.66	0.01
45	118	481.35	97	588.39	0.82	0.31
48	53	487.42	32	573.21	0.85	0.63
51	12	466.04	4	795.82	0.59	0.43

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 79.]

The endpoint of renal progression, that is the rate of loss of renal function, was determined by the slope of the reciprocal of serum creatinine (1/sCr) across time (year) during the trial. Both losartan and placebo treatment were associated with non-zero slopes and loss of renal function, however losartan-treated patients had a lower rate of loss of renal function than patients receiving placebo. Thus losartan was effective in delaying the progression of renal disease associated with type 2 diabetes mellitus (Tables 21 and 22).

Table 21. Comparison of Mean Slopes of Reciprocal of Serum Creatinine. Intent-to-Treat Analysis

Analysis of slope (dL/mg/yr)	Losartan (N=751)	Placebo (N=762)	Est. Renal Loss Reduction	p-Value*
Chronic phase(Month 3 and After)	-0.060	-0.070	13.9%	0.0033
All phases (Month 0 and After)	-0.067	-0.077	12.7%	0.0091

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 13. Negative slope indicates a loss of renal function. Est. loss reduction is estimated using a linear random effects model adjusted for region, proteinuria stratum, and baseline serum creatinine. *Based on two-sample median score nonparametric test.]

Table 22. Slopes of Reciprocal of Serum Creatinine. Intent-to-Treat Analysis

	Losartan N=751	Placebo N=762	Relative Change	p-Value
Chronic Slope (dL/mg/yr) (Month 3 and After)	n=724	n=715		
Quartiles:				
25%	-0.0990	-0.1184		
50% (Median)	-0.0541	-0.0677	20.1%	0.0010
75%	-0.0216	-0.0299		
Overall Slope (dL/mg/yr) Month 0 and After	n=748	n=756		
Quartiles:				
25%	-0.1092	-0.1237		
50% (Median)	-0.0588	-0.0693	15.07%	0.0233
75%	-0.0262	-0.0285		

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 77.]

The sponsor conducted a retrospective analysis to ascertain the effect of baseline proteinuria on the progression of renal disease by treatment (Table 23). In comparison to placebo, losartan treatment had a significant beneficial effect on the progression of renal disease only in patients who had proteinuria ≥2000 mg/gCr.

Table 23. Median of Slopes of Reciprocal of Serum Creatinine Stratified by Baseline Proteinuria. Intent-to-Treat Analysis

	Losartan N=751		Placebo N=762		Relative Change	p-Value
	n	Median	n	Median		
Overall	748	-0.0588	756	-0.0693	15.07%	0.003
Stratified (mg/gCr):						
<2000	501	-0.0433	508	-0.0457	5.18%	0.154
2000 to 3000	95	-0.0769	113	-0.0968	20.57%	0.042
≥3000	152	-0.1236	135	-0.1566	21.10%	0.019

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 78.]

The secondary endpoint of amputation added to the protocol in Amendment No. 147-02 was changed to a tertiary endpoint by Amendment No. 147-03. Losartan treatment as compared to placebo did not significantly affected the rate of amputation (Table 24).

Table 24. Tertiary Endpoint - Amputation. Intent-to-Treat Analysis

Losartan n/N (%)	Placebo n/N (%)	Est. Risk Reduction	95% Confidence Interval	p-Value
46/751 (6.1)	41/762 (5.4)	-13.5%	(-73%, 25.5%)	0.555

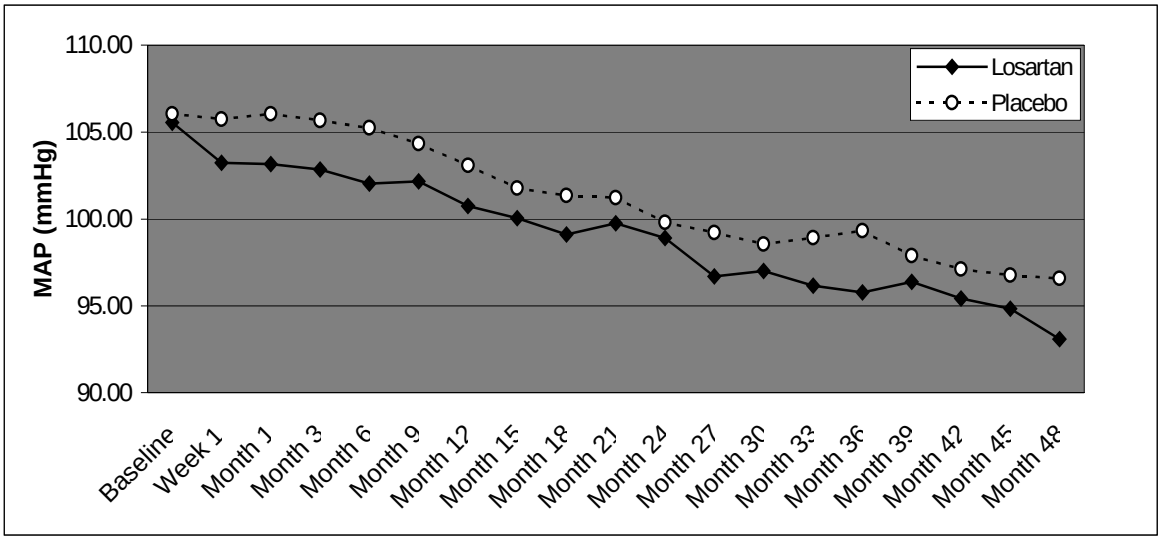
[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 23.]

Health-related quality of life (SF-36 and EQ5D) data were collected at each quarterly visit for patients who were randomized to treatment in the United States. Both treatment groups showed a reduction in health-related

quality of life over the course of the study. Noteworthy, as compared with placebo, losartan treatment failed to improve quality of life.

With the exception of ACE inhibitors and angiotensin II receptor antagonists, use of adjunctive antihypertensive agents was permitted throughout the trial in order to maintain blood pressure within the pre-specified target (BP <140/90 mmHg). Moreover, the trial was designed to attain equal degrees of blood pressure control in both treatment groups. Blood pressure decreased from baseline in both groups (Figure 10). However, review of the data for mean arterial blood pressure reveals that blood pressure control was dissimilar between the groups (Table 25). In particular, the control (i.e., reduction) of blood pressure in losartan-treated subjects was significantly better than that achieved in the placebo group (range -0.89 to -3.55 mmHg, mean (±SD) -2.29 (±0.74) mmHg).

Figure 10. Mean Arterial Blood Pressure over Time by Treatment Group. Intent-to-Treat Analysis



[FDA's analysis. Adapted from NDA 20-386/SE1-028, Protocol No. 147, Table 29.]

Table 25. Mean Arterial Blood Pressure. Intent-to-Treat Analysis

Time	Losartan			Placebo			Mean Difference (Losartan-Placebo)	p-Value
	n	Mean	SD	n	Mean	SD		
Baseline	751	105.53	10.92	762	106.03	11.60	-0.50	0.387
Week 1	731	103.24	11.47	738	105.74	11.86	-2.50	<0.001
Month 1	721	103.16	11.79	732	106.03	12.00	-2.87	<0.001
Month 3	734	102.84	12.62	731	105.66	12.01	-2.81	<0.001
Month 6	714	102.04	11.45	705	105.24	11.52	-3.20	<0.001
Month 9	691	102.17	12.04	670	104.35	11.75	-2.17	<0.001
Month 12	662	100.75	11.50	641	103.09	11.45	-2.34	<0.001
Month 15	617	100.05	11.03	599	101.78	10.79	-1.74	0.006
Month 18	589	99.10	11.09	553	101.35	10.96	-2.25	<0.001
Month 21	559	99.75	12.24	523	101.22	10.30	-1.48	0.033
Month 24	529	98.91	11.30	491	99.80	10.33	-0.89	0.192
Month 27	498	96.69	10.30	453	99.22	10.26	-2.52	<0.001
Month 30	443	97.00	10.39	401	98.55	10.07	-1.55	0.028
Month 33	374	96.15	10.81	320	98.92	10.63	-2.77	<0.001
Month 36	295	95.77	10.10	247	99.32	10.14	-3.55	<0.001

Table 25. Cont'd

Month 39	226	96.37	10.14	185	97.89	9.82	-1.51	0.128
Month 42	164	95.42	9.49	133	97.11	9.92	-1.69	0.136
Month 45	101	94.83	9.79	86	96.77	10.06	-1.93	0.186
Month 48	44	93.07	10.48	30	96.58	7.31	-3.51	0.117

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 29. SD denotes standard deviation.]

Diabetic control, as assessed by HbA_{1c} levels, was similar among the groups. Furthermore, the levels of HbA_{1c} did not change significantly over time in either treatment group (Table 26).

Table 26. Mean Hemoglobin A_{1C} (%) Prior to Primary Endpoint. Intent-to-Treat Analysis⊥

Time Point	Losartan			Placebo			Mean Diff.*	p-Value
	n	Mean	SD	n	Mean	SD		
Baseline	742	8.53	1.65	754	8.43	1.60	0.10	0.248
Month 6	632	8.61	1.79	638	8.55	1.74	0.06	0.542
Month 12	629	8.54	1.68	604	8.53	1.67	0.02	0.872
Month 18	525	8.69	1.84	504	8.58	1.75	0.11	0.315
Month 24	498	8.55	1.64	465	8.51	1.74	0.03	0.769
Month 30	394	8.53	1.64	355	8.50	1.70	0.02	0.842
Month 36	285	8.33	1.58	238	8.36	1.58	-0.03	0.836
Month 42	169	8.42	1.60	122	8.52	1.56	-0.10	0.602
Month 48	52	8.21	1.88	34	8.33	2.00	-0.12	0.780

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 30. SD denotes standard deviation. *Mean difference (Losartan-Placebo). ⊥Using last-observation-carried-forward approach.]

Pharmacokinetic/Pharmacodynamic Results: not applicable.

Safety Results: The safety of losartan compared to placebo was characterized by evaluating the following: the incidence of clinical and laboratory adverse experiences; mean changes in vital signs, and ECG parameters. All nonserious and serious adverse experiences reported during the double-blind period were included in the safety evaluation.

Table 27 summarizes the number (%) of subjects with adverse experiences, serious adverse events, discontinuations due to adverse events and deaths regardless causality for both groups. Ninety-five percent of the subjects from either group experience at least an adverse event during the trial. Similar overall incidence rates for death and serious adverse events were observed for both groups. More patients receiving placebo discontinued the trial because of adverse events, including serious adverse experiences, than those subjects treated with losartan.

Table 27. Clinical Adverse Experience Summary.[25]

	Losartan N=751 n (%)	Placebo N=762 n (%)
With one or more adverse experiences	716 (95.3)	729 (95.7)
With serious adverse experiences	481 (64.0)	487 (63.9)
Who diedI	68 (9.1)	70 (9.2)
Discontinued due to adverse experiences	143 (19.0)	185 (24.3)
Discontinued due to serious adverse experiences	107 (14.2)	141 (18.5)

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 49. IThese are deaths that occurred while patients were on double-blind study drug or 14 days after discontinuation of therapy.]

[25] Adverse events reported while patients were on double-blind study drug or within 14 days of discontinuation of therapy.

Deaths: The number of subjects who died during and post double-blind therapy up to 14 days of discontinuation of drug was similar between the groups, 68 subjects in the losartan group and 70 subjects in the placebo group. Likewise, the total number of subjects who died throughout the trial, i.e., regardless of whether on treatment or not, was not different between groups, 158 (21.0%) deaths in the losartan group *vs.* 155 (20.3%) deaths in the placebo group.[26] The most common causes of death in the losartan and placebo groups were myocardial infarction (2.0% *vs.* 2.1%, combining acute myocardial infarction and myocardial infarction together). unknown cause of death (1.5% *vs.* 0.7%), congestive heart failure (0.7% *vs*. 0.7%). cerebrovascular accident (0.7% versus 0.3%), and pneumonia (0.7% *vs*. 0.3%).

Serious Adverse Events: The frequency for the most serious adverse events (≥0.5%) reported is shown by treatment group in Table 2A (Appendix). Subjects in the Losartan group had more serious events of hypotension, 15 (2.0) *vs.* 4 (0.5), hyperkalemia, 17 (2.3) *vs.* 10 (1.3) and hypoglycemia, 37 (4.9) *vs.* 21 (2.8) and fewer cases of end-stage renal disease 76 (10.1) *vs.* 101 (13.3) than subjects receiving placebo. Otherwise, no major differences among the groups seem apparent, that may be the result of the small number of serious adverse events reported in each category.

Clinical Adverse Events: Table 3A (Appendix) summarizes the most common clinical adverse events (≥ 2.0% of subjects in any treatment group) reported during and up to 14 days post double-blind therapy. In comparison to placebo-treated subjects, subjects receiving losartan had a higher incidence of asthenia/fatigue 107 (14.2) *vs.* 78, (10.2), chest pain 93 (12.4) *vs.* 64 (8.4), hypotension 54 (7.2) *vs.* 26, (3.4), orthostatic hypotension 31 (4.1) *vs.* 10 (1.3), diarrhea 113 (15.0) *vs.* 78 (10.2), anemia 111 (14.8) *vs.* 90 (11.8), and hyperkalemia, 50 (6.7) *vs.* 24 (3.1).

Laboratory Adverse Events: Table 28 summarizes the number (%) of patients with specific laboratory adverse experiences leading to discontinuation by laboratory test. Twice as many patients receiving losartan as compared with placebo were discontinued because of hyperkalemia, 8 (1.1%) vs. 4 (0.5%).

Table 28. Number (%) of Patients With Specific Laboratory Adverse Experiences Leading to Discontinuation by Laboratory Test (Incidence >0.0%)

Parameter	Losartan N=751 n/m (%)	Placebo N=762 n/m (%)
Blood Chemistry	20/750 (2.7)	15/761 (2.0)
Carbon dioxide partial pressure decreased	1/748 (0.1)	1/756 (0.1)
Hyperglycemia	0/748 (0.0)	1/756 (0.1)
Hyperkalemia	8/748 (1.1)	4/756 (0.5)
Serum creatinine increased	11/748 (1.5)	9/756 (1.2)
Urinalysis	0/739 (0.0)	1/738 (0.1)
Proteinuria	0/695 (0.0)	1/692 (0.1)

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 64. n/m = Number of patients with laboratory adverse experiences/number of patients for whom the laboratory test was recorded.]

The number (%) of subjects (≥0.0%) with treatment-emergent laboratory adverse events during and up to 14 days post double-blind therapy by body system, primary term, and treatment regimen is presented in Table 4A (Appendix). Patients with one or more laboratory adverse experiences, 371/750 (49.5%) in the losartan group and 323/761 (42.4%) in the placebo group. The following laboratories adverse events were more commonly reported in losartan-treated subjects than in subjects receiving placebo: alanine aminotransferase increased 9 (1.3%) *vs*. 2 (0.3%), hyperkalemia 152 (20.3%) *vs.* 76 (10.1%), hematocrit decreased 35 (5.1%) *vs.* 25 (3.6%), and hemoglobin decreased 47 (6.8%) *vs.* 29 (4.2%).

Vital Signs and ECG Parameters:[27] Blood pressure decreased from baseline in both groups (Figure 10 and Table 25). However, mean arterial pressure in losartan-treated subjects was significantly lower than that

[26] The adverse experiences leading to death during the double blind treatment are listed in Table 57, NDA 20-386/SE1-028, Protocol No. 147.
[27] NDA 20-386/SE1-028, Protocol No. 147, Tables 71 and 72.

observed in the placebo group (range -0.89 to -3.55 mmHg, mean (±SD) -2.29 (±0.74) mmHg). There were no corresponding increases in mean groups heart rate. No changes in respiratory rate or weight were observed.

Review of results on mean changes from baseline to last on-treatment value for EGG parameters, i.e., atrial and ventricular rates, PR interval, QRS interval and QTc interval indicates that there no significant differences between groups.

APPENDIX

Schedule of Clinical Observations and Laboratory Measurements

	Screening(a)					Double-Blind																
Week (W)/Month (M)	W	W	W	W	W	Day	W	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
	-6[a]	-5	-3	-2	-1	1	1	1	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Informed consent	X																					
Discontinue ACE inhibitor (ACEI) or angiotensin II receptor antagonist (AIIA) therapy	X																					
Urine protein dipstick (b)	X																					
Medical history					X																	
Physical exam					X							X				X				X		X
Electrocardiogram					X							X				X				X		X
X=Partial chem. See (c). $X^{\dagger}$=Complete chem.	X	X	X	$X^{\dagger}$			X	X	X	X	X	$X^{\dagger}$	X	X	X	$X^{\dagger}$	X	X	X	$X^{\dagger}$	X	$X^{\dagger}$
X = Hematology, glycosylated hemoglobin A_{1c} (HbA_{1c}) and urinary albumin (U/A) with microscopy. $X^{\dagger}$=HbA_{1c} only. See (c) and (d).				X						$X^{\dagger}$		X		$X^{\dagger}$		X		$X^{\ddagger}$		X		X
X=Lp(a). See(c). (x)=ACE genotype						X (x)						X										X
First morning void. (e) (x)=24-hr urine subset (e)		X (x)	X (x)	X (x)	X (x)				X (x)	X (x)	X (x)	X (x)	X (x)	X (x)	X (x)	X (x)	X (x)	X (x)	X (x)	X (x)	X (x)	X (x)
X=blood pressure (BP)/heart rate (HR). ($X^{\dagger}$=Meas. peak BP also, 4 to 6 hrs postdose). See (f) re: early titration.	X	X	X	X	X	$X^{\dagger}$	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense double-blind med. $X^{\dagger}$ = see (g) for titration steps						X	$X^{\dagger}$	$X^{\dagger}$	X	X	X	X	X	X	X	X	X	X	X	X	X	
Add open-label antihtn. to pts. not controlled on 2 tabs/day of double-blind med.									X	X	X	X	X	X	X	X	X	X	X	X	X	
Assess adverse experiences (AEs)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Healthcare utilization							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Schedule of Clinical Observations and Laboratory Measurements

	Screening(a)					Double-Blind																
Week (W)/Month (M)	W	W	W	W	W	Day	W	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
	-6[a]	-5	-3	-2	-1	1	1	1	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Quality of life						X			X	X	X	X	X	X	X	X	X	X	X	X	X	X

(a) Week-6: All patients signed the informed consent and had their urine measured for protein by dipstick. Blood pressure and a partial chemistry panel were done provided the dipstick for urine protein was ≥1+. Patients without ≥1+ protein on dipstick did not enter the screening period. ACEI† washout: Patients entered a 6-week washout/screening period. For patients on prior ACE inhibitor therapy (i.e., for 5 years or less and have been taking their ACE inhibitor during the 4 weeks prior to the initial visit), the ACE inhibitor was discontinued for 6 weeks prior to randomization. Other conventional antihypertensive therapy was continued or added to replace the ACE inhibitor. Patients were then seen at Weeks -5, -3, -2, and -1 for screening procedures and blood pressure monitoring. Non-ACEI patients: These patients entered a 3-week screening period. Patients who were NOT receiving ACE inhibitor therapy at all or who did not receive ACE inhibitor therapy within 4 weeks prior to the initial visit continued their conventional antihypertensive therapy. After completing the initial visit procedures, these patients returned 1 week later for Visit 4 (Week -2). Visits 2 and 3 were omitted.
Week -1: Medical history and physical exam were performed for patients with at least 2 qualifying serum creatinine and urinary albumin/creatinine ratio (UA/Cr) results during the screening period. In patients with only 1 qualifying serum creatinine or UA/Cr, the medical history and physical exam were deferred until 2 qualifying serum creatinine and 2 qualifying UA/Cr measurements were obtained.
Laboratory measurements at Week -1: If necessary, a partial chemistry for serum creatinine or a first morning void for UA/Cr was measured only if a qualifying result was still needed for the patient to qualify. Pregnancy test for females of childbearing potential had to be done within ~72 hours prior to randomization.
(b) Urine dipstick: Urine dipstick at Visit 1 must have been ≥1+ for protein to continue in the screening period.
(c) Labs: A central lab measured serum chemistry, hematology and pregnancy test. All labs were to be done in the morning following an overnight fast. Serum creatinine was required to be 1.3 to 3.0 mg/dL (115 to 265 µmol/L) on 2 occasions during the screening period; 1.5-3.0 mg/dL for male patients >132 lbs. [60 kg]). The Week -3 partial chemistry was only necessary if additional qualifying serum creatinine levels were required.
Lp(a): this lipoprotein was assessed in U.S. and European sites only. The blood specimen was sent to the central lab.
(d) Urinalysis: Urinalysis with microscopy was not measured by the central lab but by the investigator's local lab.
(e) First morning void: UA/Cr was analyzed by the central lab. Patients must have had at least 2 first morning urine samples ≥300 mg/g (≥25 mg/mmol) ~1 week apart during screening to be eligible for the study. It was not necessary to collect more than 3 samples provided 2 qualify. Option: extend the screening period 1 or 2 weeks to obtain additional samples in order to qualify the patient.
Twenty-four hour urine substudy: Twenty-four hour urine was done in a subset of the population.
(f) Blood Pressure: Early titration: Patients with diastolic BP ≥105 mm Hg anytime during the first 4 weeks after randomization must have had double-blind medication titrated up to 2 tablets daily from Bottle A and extra clinic visits scheduled weekly to monitor blood pressure.
(g) Dose Titration: The starting double-blind dose was 1 tablet daily from Bottle A (losartan 50 mg or placebo). At the investigator's discretion, in patients with possible depletion of intravascular volume (e.g., due to high-dose diuretic) or with a history of orthostatic hypotension, the starting dose may have been 1 tablet daily from Bottle B, which contained losartan 25 mg or placebo.
Double-blind medication was added to each patient's conventional antihypertensive therapy.
Week One: Any patient started on 1 tablet daily from Bottle B (losartan 25 mg or placebo) should have been titrated up to 1 tablet daily from Bottle A (losartan 50 mg or placebo). Patients who did not tolerate the increase due to symptomatic hypotension may have remained on 1 tablet daily from Bottle B (losartan 25 mg or placebo) provided their concomitant open-label antihypertensive medication had been reduced or discontinued first, if possible.
Month One: The investigator was to make every effort to control blood pressure (BP <140/90 mm Hg) by using 1 or 2 tablets daily from Bottle A (losartan 50 mg or placebo) and reducing or discontinuing concomitant open-label antihypertensive medication whenever possible.
† Patients on an angiotensin II antagonist (AIIA) also required the 6-week washout period.

Data Source: [3.3]

Table 1A. Number of Patients Discontinued Study Therapy by Treatment and Region

Region	Reason for Discontinuation	Losartan			Placebo			Total		
		N	n	%	N	n	%	N	n	%
Asia	Clinical AE	125	25	20.0%	132	37	28.0%	257	62	24.1%
	Laboratory AE				132	2	1.5%	257	2	0.8%
	Other Reason	125	4	3.2%	132	10	7.6%	257	14	5.4%
	Moved	125	1	0.8%				257	1	0.4%
	Withdrawn	125	2	1.6%	132	11	8.3%	257	13	5.1%
	Protocol Violation	125	1	0.8%				257	1	0.4%
	All Reason	**125**	**33**	**26.4%**	**132**	**60**	**45.5%**	**257**	**93**	**36.2%**
Europe	Clinical AE	151	50	33.1%	144	53	36.8%	295	103	34.9%
	Laboratory AE				144	3	2.1%	295	3	1.0%
	Other Reason	151	9	6.0%	144	6	4.2%	295	15	5.1%
	Withdrawn	151	10	6.6%	144	8	5.6%	295	18	6.1%
	Protocol Violation				144	1	0.7%	295	1	0.3%
	All Reason	**151**	**69**	**45.7%**	**144**	**71**	**49.3%**	**295**	**140**	**47.5%**
Latin America	Clinical AE	137	39	28.5%	137	40	29.2%	274	79	28.8%
	Laboratory AE	137	6	4.4%	137	4	2.9%	274	10	3.6%
	Other Reason	137	9	6.6%	137	9	6.6%	274	18	6.6%
	Moved	137	1	0.7%	137	1	0.7%	274	2	0.7%
	Withdrawn	137	6	4.4%	137	8	5.8%	274	14	5.1%
	Protocol Violation				137	1	0.7%	274	1	0.4%
	All Reason	**137**	**61**	**44.5%**	**137**	**63**	**46.0%**	**274**	**124**	**45.3%**
North America	Clinical AE	338	85	25.1%	349	112	32.1%	687	197	28.7%
	Laboratory AE	338	14	4.1%	349	7	2.0%	687	21	3.1%
	Other Reason	338	39	11.5%	349	56	16.0%	687	95	13.8%
	Moved	338	3	0.9%				687	3	0.4%
	Withdrawn	338	39	11.5%	349	33	9.5%	687	72	10.5%
	Protocol Violation	338	1	0.3%	349	1	0.3%	687	2	0.3%
	All Reason	**338**	**181**	**53.6%**	**349**	**209**	**59.9%**	**687**	**390**	**56.8%**
Total	Clinical AE	751	199	26.5%	762	242	31.8%	1513	441	29.1%
	Laboratory AE	751	20	2.7%	762	16	2.1%	1513	36	2.4%
	Other Reason	751	61	8.1%	762	81	10.6%	1513	142	9.4%
	Moved	751	5	0.7%	762	1	0.1%	1513	6	0.4%
	Withdrawn	751	57	7.6%	762	60	7.9%	1513	117	7.7%
	Protocol Violation	751	2	0.3%	762	3	0.4%	1513	5	0.3%
	All Reason	**751**	**344**	**45.8%**	**762**	**403**	**52.9%**	**1513**	**747**	**49.4%**

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Response to FDA's request dated February 27, 2002. N: Number of patients by treatment and region. n: Number of patients who discontinued study therapy by treatment and region. %: percentage of patients who discontinued study therapy by treatment and region.]

Table 2A. Number (%) of Patients With Specific Serious Clinical Adverse Experiences (Incidence >0.5% in One or More Treatment Groups) by Body System

Adverse Event	Losartan N=751 n (%)	Placebo N=762 n (%)
Body as a Whole/Site Unspecified	112 (14.9)	107 (14.0)
Bacterial sepsis	8 (1.1)	11 (1.4)
Cardiopulmonary failure	0 (0.0)	4 (0.5)
Chest pain	18 (2.4)	16 (2.1)
Dehydration	9 (1.2)	13 (1.7)
Dizziness	7 (0.9)	5 (0.7)
Edema	6 (0.8)	4 (0.5)
Fluid overload	3 (0.4)	4 (0.5)
Syncope	6 (0.8)	5 (0.7)
Trauma	5 (0.7)	3 (0.4)

Table 2A. Cont'd

Unknown cause of death	11 (1.5)	5 (0.7)
Cardiovascular System	257 (34.2)	285 (37.4)
Acute myocardial infarction	14 (1.9)	15 (2.0)
Angina pectoris	7 (0.9)	15 (2.0)
Arrhythmia	4 (0.5)	2 (0.3)
Atrial fibrillation	9 (1.2)	7 (0.9)
Bradycardia	13 (1.7)	4 (0.5)
Cardiac arrest	9 (1.2)	8 (1.0)
Cardiogenic shock	4 (0.5)	6 (0.8)
Carotid artery obstruction	3 (0.4)	4 (0.5)
Cerebral infarction	4 (0.5)	5 (0.7)
Cerebrovascular accident	36 (4.8)	34 (4.5)
Heart failureH	85 (11.4)	100 (13.1)
Coronary artery disease	17 (2.3)	26 (3.4)
Deep vein thrombosis	4 (0.5)	4 (0.5)
Gangrene	11 (1.5)	8 (1.0)
Hypertension	11 (1.5)	8 (1.0)
Hypertensive crisis	4 (0.5)	4 (0.5)
Hypotension	15 (2.0)	4 (0.5)
Ischemic heart disease	3 (0.4)	10 (1.3)
Myocardial infarctionI	59 (7.9)	67 (8.8)
Pericarditis	0 (0.0)	4 (0.5)
Peripheral vascular disorder	9 (1.2)	8 (1.0)
Pulmonary edema	6 (0.8)	10 (1.3)
Sinus bradycardia	5 (0.7)	3 (0.4)
Third degree atrioventricular block	6 (0.8)	2 (0.3)
Unstable angina	24 (3.2)	32 (4.2)
Vascular graft occlusion	4 (0.5)	1 (0.1)
Digestive System	70 (9.3)	63 (8.3)
Diarrhea	5 (0.7)	4 (0.5)
Gastric ulcer	4 (0.5)	1 (0.1)
Gastritis	5 (0.7)	3 (0.4)
Gastroenteritis	5 (0.7)	9 (1.2)
Gastrointestinal bleeding	8 (1.1)	8 (1.0)
Intestinal vascular insufficiency	5 (0.7)	2 (0.3)
Paralytic ileus	4 (0.5)	4 (0.5)
Vomiting	4 (0.5)	2 (0.3)
Endocrine System	53 (7.1)	52 (6.8)
Diabetic gastroparesis	0 (0.0)	4 (0.5)
Diabetic ketoacidosis	4 (0.5)	3 (0.4)
Diabetic vascular disease	30 (4.0)	28 (3.7)
Loss o f diabetic control	21 (2.8)	15 (2.0)
Eyes, Ears, Nose, and Throat	34 (4.5)	33 (4.3)
Cataract	9 (1.2)	7 (0.9)
Diabetic retinopathy	3 (0.4)	4 (0.5)
Hemic and Lymphatic System	29 (3.9)	22 (2.9)
Anemia	25 (3.3)	19 (2.5)
Hepatobiliary System	8 (1.1)	12 (1.6)
Cholecystitis	1 (0.1)	7 (0.9)

Table 2A. Cont'd

Cholelithiasis	5 (0.7)	3 (0.4)
Immune System	3 (0.4)	3 (0.4)
Metabolism and Nutrition	70 (9.3)	60 (7.9)
Hyperglycemia	17 (2.3)	23 (3.0)
Hyperkalemia	17 (2.3)	10 (1.3)
Hypoglycemia	37 (4.9)	21 (2.8)
Hypokalemia	3 (0.4)	4 (0.5)
Musculoskeletal System	58 (7.7)	53 (7.0)
Femur fracture	3 (0.4)	6 (0.8)
Gout	3 (0.4)	4 (0.5)
Humeral fracture	4 (0.5)	0 (0.0)
Osteomyelitis	14 (1.9)	13 (1.7)
Nervous System	27 (3.6)	24 (3.1)
Psychiatric Disorder	5 (0.7)	6 (0.8)
Respiratory System	91 (12.1)	80 (10.5)
Asthma	4 (0.5)	2 (0.3)
Bronchitis	8 (1.1)	10 (1.3)
Dyspnea	8 (1.1)	4 (0.5)
Lower respiratory infection	8 (1.1)	2 (0.3)
Pleural effusion	3 (0.4)	6 (0.8)
Pneumonia	46 (6.1)	46 (6.0)
Respiratory failure	7 (0.9)	4 (0.5)
Respiratory insufficiency	1 (0.1)	4 (0.5)
Skin and Skin Appendages	41 (5.5)	44 (5.8)
Basal cell carcinoma	4 (0.5)	8 (1.0)
Cellulitis	23 (3.1)	25 (3.3)
Erysipelas	4 (0.5)	0 (0.0)
Urogenital System	167 (22.2)	178 (23.4)
Acute renal failure§	12 (1.6)	12 (1.5)
Chronic renal failure	17 (2.3)	20 (2.6)
Dialysis vascular access complication	3 (0.4)	4 (0.5)
End-stage renal disease	76 (10.1)	101 (13.3)
Pyelonephritis	2 (0.3)	4 (0.5)
Renal insufficiency	54 (7.2)	53 (7.0)
Urinary tract infection	13 (1.7)	7 (0.9)

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 49. HHeart failure includes congestive heart failure, 83 (11.1) and 98 (12.9), and left cardiac failure2 (0.3) and 2 (0.3). IMyocardial infarction (MI) includes acute MI, 14 (1.9) and 15 (2.0); age indeterminate MI, 0 (0.0) and 1 (0.1); MI, 35 (4.7) and 45 (5.9); myocardial reinfarction, 1 (0.1) and 1 (0.1); non-Q- wave MI, 3 (0.4) and 5 (0.7); and Q-wave MI, 1 (0.1) and 0 (0.0). §Acute renal failure includes acute tubular necrosis, 0 (0.0) and 1 (0.1), and acute renal failure, 12 (1.6) and 11 (1.4). &Renal insufficiency includes renal failure, 12 (1.6) and 12 (1.6), and renal insufficiency, 42 (5.6) and 41 (5.4). Although a patient may have had 2 or more serious clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.]

Table 3A. Number (%) of Patients with Clinical Adverse Experiences (Incidence ≥2%) by Body System

Body System/Adverse Event	Losartan N=751		Placebo N=762	
	n	(%)	n	(%)
Body as a Whole/Site Unspecified	535	(71.2)	551	(72.3)
Abdominal pain	39	(5.2)	47	(6.2)
Asthenia/fatigue	107	(14.2)	78	(10.2)

Table 3A. Cont'd

Chest pain	93	(12.4)	64	(8.4)
Contusion	16	(2.1)	21	(2.8)
Dehydration	23	(3.1)	30	(3.9)
Dizziness	130	(17.3)	130	(17.1)
EdemaH	146	(32.8)	177	(36.0)
Fever	29	(3.9)	22	(2.9)
Fungal infection	14	(1.9)	24	(3.1)
Infection	37	(4.9)	31	(4.1)
Influenza-like disease	76	(10.1)	66	(8.7)
Malaise	14	(1.9)	19	(2.5)
Pain	31	(4.1)	28	(3.7)
Syncope	22	(2.9)	11	(1.4)
Trauma	33	(4.4)	25	(3.3)
Upper respiratory infection	184	(24.5)	192	(25.2)
Cardiovascular System	471	(62.7)	491	(64.4)
Angina pectoris	25	(3.3)	35	(4.6)
Atria] fibrillation	24	(3.2)	17	(2.2)
Blood pressure increased	13	(1.7)	18	(2.4)
Bradycardia	22	(2.9)	16	(2.1)
Bruit	22	(2.9)	26	(3.4)
Cerebrovascular accident	37	(4.9)	36	(4.7)
Heart failure#	105	(13.9)	130	(17.0)
Coronary artery disease	25	(3.3)	31	(4.1)
First degree atrioventricular block	22	(2.9)	13	(1.7)
Hypertension	90	(12.0)	IIO	(14.4)
Hypotension	54	(7.2)	26	(3.4)
Ischemic heart disease	9	(1.2)	18	(2.4)
Left atrial hypertrophy	4	(0.5)	15	(2.0)
Left ventricular hypertrophy	14	(1.9)	20	(2.6)
Myocardial infarctionэ	66	(8.8)	86	(11.3)
Nonspecific ST-T change	11	(1.5)	23	(3.0)
Orthostatic hypotension	31	(4.1)	10	(1.3)
Palpitation	20	(2.7)	14	(1.8)
Peripheral vascular disorder	18	(2.4)	17	(2.2)
Premature ventricular contraction	16	(2.1)	18	(2.4)
Sinus bradycardia	17	(2.3)	19	(2.5)
Tachycardia	16	(2.1)	40	(1.3)
Unstable angina	24	(3.2)	33	(4.3)
Digestive System	372	(49.5)	347	(45.5)
Constipation	74	(9.9)	76	(10.0)
Dental pain	15	(2.0)	9	(1.2)
Diarrhea	113	(15.0)	78	(10.2)
Dyspepsia	31	(4.1)	25	(3.3)
Epigastric discomfort	20	(2.7)	22	(2.9)
Gastritis	37	(4.9)	28	(3.7)
Gastroenteritis	20	(2.7)	20	(2.6)
Nausea	75	(10.0)	80	(10.5)
Vomiting	56	(7.5)	56	(7.3)
Endocrine System	156	(20.8)	150	(19.7)
Diabetic neuropathy	27	(3.6)	21	(2.8)
Diabetic vascular disease	77	(10.3)	71	(9.3)
Hypothyroidism	17	(2.3)	15	(2.0)
Loss of diabetic control	38	(5.1)	43	(5.6)
Eyes, Ears, Nose, and Throat	307	(40.9)	294	(38.6)
Blurred vision	18	(2.4)	13	(1.7)
Cataract	49	(6.5)	39	(5.1)
Diabetic retinopathyI	44	(5.8)	47	(6.2)

Table 3A. Cont'd

Epistaxis	19	(2.5)	18	(2.4)
Ophthalmic hemorrhage	15	(2.0)	14	(1.8)
Otitis	15	(2.0)	7	(0.9)
Pharyngitis	33	(4.4)	45	(5.9)
Vitreous hemorrhage	21	(2.8)	18	(2.4)
Sinusitis	45	(6.0)	38	(5.0)
Hemic and Lymphatic System	121	(16.1)	98	(12.9)
Anemia&	111	(14.8)	90	(11.8)
Hepatobiliary System	29	(3.9)	33	(4.3)
Cholelithiasis	15	(2.0)	12	(1.6)
Immune System	13	(1.7)	17	(2.2)
Metabolism and Nutrition	264	(35.2)	250	(32.8)
Anorexia	13	(1.7)	17	(2.2)
Hypercholesterolemia	18	(2.4)	20	(2.6)
Hyperglycemia	34	(4.5)	37	(4.9)
Hyperkalemia	50	(6.7)	24	(3.1)
Hyperlipidemia	20	(2.7)	27	(3.5)
Hyperuricemia	10	(1.3)	16	(2.1)
Hypoglycemia	105	(14.0)	79	(10.4)
Hypokalemia	18	(2.4)	20	(2.6)
Weight Gain	32	(4.3)	26	(3.4)
Musculoskeletal System	365	(48.6)	351	(46.1)
Arthralgia	17	(2.3)	19	(2.5)
Arthritis	17	(2.3)	21	(2.8)
Back pain	93	(12.4)	73	(9.6)
Foot pain	23	(3.1)	22	(2.9)
Gout	41	(5.5)	46	(6.0)
Hip pain	16	(2.1)	16	(2.1)
Knee pain	37	(4.9)	31	(4.1)
Leg pain	39	(5.2)	28	(3.7)
Muscular cramp	48	(6.4)	55	(7.2)
Muscular weakness	50	(6.7)	31	(4.1)
Musculoskeletal pain	16	(2.1)	10	(1.3)
Myalgia	14	(1.9)	19	(2.5)
Neck pain	13	(1.7)	24	(3.1)
Osteomyelitis	14	(1.9)	15	(2.0)
Shoulder pain	33	(4.4)	34	(4.5)
Nervous System	229	(30.5)	270	(35.4)
Headache	70	(9.3)	94	(12.3)
Hypesthesia	34	(4.5)	31	(4.1)
Insomnia	29	(3.9)	53	(7.0)
Paresthesia	14	(1.9)	17	(2.2)
Peripheral neuropathy	20	(2.7)	25	(3.3)
Somnolence	15	(2.0)	15	(2.0)
Vertigo	21	(2.8)	21	(2.8)
Psychiatric Disorder	81	(10.8)	77	(10.1)
Anxiety	22	(2.9)	23	(3.0)
Depression	41	(5.5)	44	(5.8)
Respiratory System	286	(38.1)	275	(36.1)
Bronchitis	74	(9.9)	69	(9.1)
Cough	83	(11.1)	80	(10.5)
Dyspnea	95	(12.6)	99	(13.0)
Lower respiratory infection	17	(2.3)	10	(1.3)
Pneumonia	58	(7.7)	62	(8.1)
Skin and Skin Appendages	252	(33.6)	268	(35.2)

Table 3A. Cont'd

Blister	20	(2.7)	8	(1.0)
Eczematous dermatitis	14	(1.9)	20	(2.6)
Cellulitis	53	(7.1)	47	(6.2)
Pruritus	46	(6.1)	50	(6.6)
Skin ulcer	13	(1.7)	19	(2.5)
Rash	53	(7.1)	55	(7.2)
Urogenital System	315	(41.9)	345	(45.3)
Chronic renal failure	20	(2.7)	27	(3.5)
End-stage renal disease	76	(10.1)	101	(13.3)
Renal insufficiency–	82	(10.9)	96	(12.6)
Urinary tract infection	120	(16.0)	100	(13.1)

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 51. HEdema includes edema, 64 (8.5) and 72 (9.4); Lower extremity edema 159 (21.2) and 184 (24.1); and peripheral edema 23 (3.1) and 19 (2.5). #Heart failure includes congestive heart failure, 101 (13.4) and 126 (16.5) and left cardiac failure, 4 (0.5) and 4 (0.5). § Myocardial infarction (MI) includes acute MI, 14 (1.9) and 16 (2.1); age indeterminate MI, 8 (1.1) and 13 (1.7); MI, 39 (5.2) and 51 (6.7); myocardial reinfarction, 1 (0.1) and 1 (0.1); non-Q-wave MI, 3 (0.4) and 5 (0.7); and Q-wave MI, 1 (0.1) and 2 (0.3). IDiabetic retinopathy includes diabetic retinopathy, 37 (4.9) and 35 (4.6), and retinopathy, 7 (0.9) and 12 (1.6). &Anemia includes anemia, 106 (14.1) and 82 (10.8); anemia of uremia, 0 (0.0) and 3 (0.4); hemolytic anemia, 0 (0.0) and 1 (0.1); and microcytic anemia, 5 (0.7) and 4 (0.5). –Renal insufficiency includes renal insufficiency, 66 (8.8) and 77 (10.1), and renal failure, 16 (2.1) and 19 (2.5). Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.]

Table 4A. Number (%) of Patients with Laboratory Experiences (Incidence ≥0.0%) by Laboratory Test Category

Laboratory Adverse Event	**Losartan N=751**		**Placebo N=762)**	
	n/m	**(%)**	**n/m**	**(%)**
Blood Chemistry	321/750	(42.8)	283/761	(37.2)
Alanine aminotransferase increased	9/687	(1.3)	2/693	(0.3)
Alkaline phosphatase increased	12/689	(1.7)	16/691	(2.3)
Amylase increased	0/2	(0.0)	1/4	(25.0)
Antihepatitis C virus antibody positive	1/4	(25.0)	0/1	(0.0)
Arterial pH increased	0/H		1/2	(50.0)
Aspartate aminotransferase increased	7/687	(1.0)	3/693	(0.4)
Bicarbonate decreased	0/6	(0.0)	1/3	(33.3)
Blood pancreatic lipase increased	0/1	(0.0)	1/1	(100.0)
Blood urea increased	1/9	(11.1)	3/7	(42.9)
Blood urea nitrogen increased	53/748	(7.1)	49/756	(6.5)
Carbon dioxide partial pressure decreased	36/748	(4.8)	20/756	(2.6)
Carbon dioxide partial pressure increased	2/748	(0.3)	7/756	(0.9)
Creatine phosphokinase increased	1/9	(11.1)	3/15	(20.0)
Creatine phosphokinase mb increased	0/4	(0.0)	1/8	(12.5)
Digoxin toxicity	1/2	(50.0)	0/2	(0.0)
Direct Coombs'test positive	1/1	(100.0)	0/H	
Fasting blood glucose increased	3/6	(50.0)	1/7	(14.3)
Ferritin decreased	1/H		0/1	(0.0)
Gamma-glutamyl transpeptidase increased	1/5	(20.0)	1/7	(14.3)
Glycosylated hemoglobin increased	38/720	(5.3)	32/716	(4.5)
Haptoglobin increased	1/1	(100.0)	0/H	
High density lipoprotein decreased	5/687	(0.7)	1/690	(0.1)
Hyperbilirubinemia	1/687	(0.1)	0/690	(0.0)
Hypercalcemia	0/688	(0.0)	4/692	(0.6)

Table 4A. Cont'd

Hyperchloremia	14/748	(1.9)	11/756	(1.5)
Hypercholesterolemia	27/690	(3.9)	48/691	(6.9)
Hyperglycemia	62/748	(8.3)	83/756	(11.0)
Hyperkalemia	152/748	(20.3)	76/756	(10.1)
Hypernatremia	7/748	(0.9)	4/756	(0.5)
Hyperphosphatemia	9/688	(1.3)	19/691	(2.7)
Hyperproteinemia	1/688	(0.1)	0/691	(0.0)
Hypertriglyceridemia	25/689	(3.6)	36/690	(5.2)
Hyperuricemia	7/748	(0.9)	7/756	(0.9)
Hypocalcemia	6/688	(0.9)	6/692	(0.9)
Hypochloremia	2/748	(0.3)	4/756	(0.5)
Hypoglycemia	7/748	(0.9)	16/756	(2.1)
Hypokalemia	10/748	(1.3)	21/756	(2.8)
Hpomagnesemia	1/3	(33.3)	0/5	(0.0)
Hyponatremia	6/748	(0.8)	8/756	(1.1)
Hypoproteinemia	1/688	(0.1)	1/691	(0.1)
Hypouricemia	1/748	(0.1)	0/756	(0.0)
Ionized calcium decreased	0/688	(0.0)	1/692	(0.1)
Ketosis	0/f		1/1	(100.0)
Lipoprotein (A) increased	0/499	(0.0)	3/500	(0.6)
Low density lipoprotein increased	14/670	(2.1)	20/673	(3.0)
Nonfasting blood glucose increased	1/748	(0.1)	0/756	(0.0)
Parathyroid hormone increased	0/2	(0.0)	2/4	(50.0)
Serum albumin decreased	5/689	(0.7)	3/690	(0.4)
Serum albumin increased	2/689	(0.3)	0/690	(0.0)
Serum creatinine decreased	0/748	(0.0)	1/756	(0.1)
Serum creatinine increased	137/748	(18.3)	139/756	(18.4)
Serum iron decreased	1/H		1/1	(100.0)
Thyroglobulin increased	0/H		1/1	(100.0)
Thyroid stimulating hormone decreased	0/13	(0.0)	2/21	(9.5)
Thyroid stimulating hormone increased	0/13	(0.0)	1/21	(4.8)
Thyroid T3 decreased	l/H		0/2	(0.0)
Thyroid T4 increased	0/4	(0.0)	2/9	(22.2)
Total serum protein decreased	0/688	(0.0)	1/691	(0.1)
Total serum protein increased	1/688	(0.1)	1/691	(0.1)
Uric acid increased	45/748	(6.0)	40/756	(5.3)
Hematology	73/694	(10.5)	49/695	(7.1)
Atypical lymphocyte	0/22	(0.0)	1/27	(3.7)
Band neutrophils increased	1/17	(5.9)	0/13	(0.0)
Direct Coombs'test positive	1/1	(100.0)	0/1	(0.0)
Eosinophils increased	9/689	(1.3)	6/684	(0.9)
Erythrocyte sedimentation rate increased	3/3	(100.0)	3/5	(60.0)
Erythrocytes decreased	4/690	(0.6)	2/691	(0.3)
Erythrocytes increased	0/690	(0.0)	1/691	(0.1)
Ferritin decreased	1/3	(33.3)	0/5	(0.0)
Hematocrit decreased	35/690	(5.1)	25/691	(3.6)
Hematocrit increased	0/690	(0.0)	3/691	(0.4)
Hemoglobin decreased	47/689	(6.8)	29/691	(4.2)
Hemoglobin increased	1/689	(0.1)	4/691	(0.6)
Leukocytes decreased	4/688	(0.6)	1/692	(0.1)
Leukocytes increased	7/688	(1.0)	6/692	(0.9)

Table 4A. Cont'd

Leukocytosis	2/688	(0.3)	1/692	(0.1)
Lymphocytes increased	1/689	(0.1)	0/685	(0.0)
Lymphocytopenia	2/689	(0.3)	2/685	(0.3)
Neutrophils increased	1/689	(0.1)	4/685	(0.6)
Platelets decreased	6/688	(0.9)	3/688	(0.4)
Platelets increased	1/688	(0.1)	0/688	(0.0)
Serum Iron decreased	1/3	(33.3)	1/4	(25.0)
Thrombocytopenia	0/688	(0.0)	1/688	(0.1)
Hemostatic Function	1/4	(25.0)	1/2	(50.0)
Partial thromboplastin time increased	0/2	(0.0)	1/2	(50.0)
Prothrombin time increased	1/3	(33.3)	1/2	(50.0)
Immunology	1/2	(50.0)	1/2	(50.0)
Antideoxyribonucleic acid antibody positive	0/H		1/1	(100.0)
Antinuclear antibody increased	0/H		1/1	(100.0)
C-Reactive protein increased	1/2	(50.0)	1/2	(50.0)
Microbiology	37/12		28/14	
Bacteriuria	37/3		28/4	
Serology	3/5	(60.0)	1/3	(33.3)
Prostate-specific antigen increased	3/5	(60.0)	1/3	(33.3)
Stool Analysis	3/3	(100.0)	3/4	(75.0)
Fecal guaiac positive	1/3	(33.3)	0/3	(0.0)
Fecal occult blood	2/3	(66.7)	3/3	100.0
Urinalysis	108/739	(14.6)	106/738	(14.4)
24 hour urinary creatinine increased	1/305	(0.3)	1/307	(0.3)
Albuminuria	1/739	(0.1)	2/738	(0.3)
Bacteriuria	37/638	(5.8)	28/623	(4.5)
Candiduria	0/H		1/1	(100.0)
Creatinine clearance decreased	0/6	(0.0)	1/8	(12.5)
Creatinine clearance increased	2/6	(33.3)	1/8	(12.5)
Crystalluria	4/627	(0.6)	4/613	(0.7)
Erythrocyturia	14/654	(2.1)	12/650	(1.8)
Glycosuria	17/652	(2.6)	21/649	(3.2)
Hematuria	13/654	(2.0)	13/650	(2.0)
Ketosis	0/1	(0.0)	1/H	
Leukocyturia	30/642	(4.7)	24/635	(3.8)
Microscopic hematuria	4/641	(0.6)	4/635	(0.6)
Proteinuria	23/695	(3.3)	35/692	(5.1)
Pyuria	4/642	(0.6)	4/635	(0.6)
Urinary albumin/creatinine ratio increased	14/738	(1.9)	21/736	(2.9)
Urinary casts	6/629	(1.0)	6/615	(1.0)
Urinary creatinine increased	0/718	(0.0)	1/719	(0.1)
Urinary epithelial cells increased	8/621	(1.3)	4/606	(0.7)
Urinary pH increased	1/646	(0.2)	2/644	(0.3)
Urinary potassium increased	1/318	(0.3)	0/318	(0.0)
Urinary renal tubular epithelial cells	2/619	(0.3)	1/611	(0.2)

[Sponsor's analysis. Source: NDA 20-386/SE1-028, Protocol No. 147, Table 60. HIndicates that there was no associated laboratory test or there were no patients for whom the laboratory test was recorded. Although a patient may have had 2 or more laboratory adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories. n/m = Number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded.]

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/s/

Juan Carlos Pelayo
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